A health economic evaluation of neurological interventions targeting epilepsy, migraine, dementia and Parkinson's disease in Ethiopia, Malawi, and the United Republic of Tanzania

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Master thesis in Global Health

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Abbreviations

ASA	Acetylsalicylic acid
BCEPS	Bergen Centre for Ethics and Priority Setting in Health
CD	Communicable diseases
CEA	Cost-effectiveness analysis
DALY	Disability-adjusted life years
DCP	Disease Control Priorities
ICER	Incremental cost-effectiveness ratio
GBD	Global Burden of Disease Study
GDP	Gross domestic product
HIC	High-income country
HLY	Healthy life year
LIC	Low-income country
LLMIC	Low- and low-to-middle-income country
LMIC	Low-and-middle-income country
MDGs	Millennium Development Goals
NCD	Non-communicable diseases
OOP	Out-of-pocket (expenditures)
Pp	Percentage points
QoL	Quality of life
SDGs	Sustainable Development Goals
UHC	Universal health coverage
WHO	World Health Organization
WTP	Willingness to pay

Structure of the thesis

The mantle of this thesis frames the paper (Hubbers, J. et al. 2022; targeted towards the journal "Neurology"; see Appendix 1) that provides a cost-effectiveness analysis performed through a modelling exercise of nine interventions targeting four neurological disorders in Ethiopia, Malawi, and the United Republic of Tanzania. As the results of the cost-effectiveness analysis, as well as an elaborate methodology can be found in the paper itself, it was chosen in this mantle to delve deeper into a global and East African perspective and to provide an elaborate justification of the methods and its considerations. Lastly, a section was added on important contextual factors that need to be considered during scale-up and implementation of the results into policy.

This thesis is structured in five sections:

1. A general introduction into neurological disorders in a global and East African perspective
2. General information on cost-effectiveness analyses, rationale, and objectives
3. A justification of the methodology, reflections and deliberations between the possible research methods and assumptions
4. Appendix 1: the paper and its supplementary file
5. Appendix 2 – 3. These appendixes were added as background information solely to clarify the disorders and provide an initial impression in FairChoices

1. Introduction: Neurological disorders in a global health landscape

1.1 Global burden and projected increase of neurological and other non-communicable diseases

The prevalence of chronic, non-communicable diseases (NCDs) is rising steadily [1-5], resulting in a high global disease burden and even higher economic consequences. Yet, key players in the global health field remain predominantly focused on curing communicable diseases (CDs), leaving the prevention of NCDs arguably as a neglected field [6, 7]. According to the Lancet NCDI Poverty Commission Study Group [7], more than a third of all disability-adjusted life years (DALYs, a measure of combining mortality and morbidity [8]) can be accounted for by NCDs and injuries. Furthermore, increased focus is needed in order to reduce the burden of NCDs in low- and lower middle-income countries (LLMICs)[9]. Globally, an increase in NCDs is projected, which will affect LLMIC settings the greatest because of the expected population growth and increased life expectancy [3, 5, 7]. Therefore, the discussion arises if we are facing an inevitable NCD-pandemic [10]. For these reasons, in

this thesis I would like to zoom in further on a cluster of NCDs, namely neurological disorders.

Neurological disorders are among the frontrunners in terms of mortality and morbidity [4] and are estimated to affect hundreds of millions of people globally [11]. The Global Burden of Disease (GBD) study revealed that in 2016, neurological disorders were the leading cause of DALYs, and were listed as the second highest cause of deaths, with neurological disorders making up for 11.6% of DALYs and 16.5% of deaths globally [3, 4, 12]. The high DALY count for neurological disorders can mainly be attributed to stroke, migraine, meningitis, and dementia [2, 12]. The GBD study in 2019 showed that neurological disorders account for 3.8% of DALYs globally when stroke, meningitis, tetanus, brain cancer, and trauma are excluded [13]. However, the burden of neurological disorders is expected to increase drastically in the upcoming years [5, 14, 15]. For example, the disease burden of Parkinson's disease is projected to increase in prevalence from 6.3 million in 2015 to 17.5 million people globally in 2040 as a result of demographic- and epidemiological transitions, as well as the effects of industrialization through pesticide use and emission of toxic gasses [16]. Similarly, the global prevalence of dementia is expected to increase by 83% between 2010 (36 million people) and 2030 (66 million people), and by 219% by 2050 to affect 115 million people [17]. The economic costs associated with Alzheimer's disease and other dementias were an estimated US$2.8 trillion in 2019, but are expected to increase to an estimated US$16.9 trillion in 2050 as a result of the expected prevalence increase.

In conclusion, the impact of the rapid increase of the global burden of neurological disorders is vast, and the direct and indirect economic costs attached to neurological disorders are rising at a staggering rate as well. Therefore, immediate global commitment is imperative.

1.2 Neurological disorders in the global health framework: current status

Exerting greater global efforts on reducing neurological disorders, via prevention or equitable access to health services, can achieve a vast impact, aligning well with the current global health agenda.

In 2015, the global health field was reframed by the sustainable development goals (SDGs), targeting the unfinished agenda of its predecessor, the Millennium Development Goals (MDGs). The SDGs have provided direction for global collaboration in terms of health, poverty reduction and reducing inequalities [18]. Within this agenda, health serves as a core element, as well as a particular focus on reducing the burden of NCDs and achieving universal health coverage, as listed below:

- SDG 3, target 4: *"By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being" [18]*.

- SDG 3, target 8: "*Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all" [18]*.

Enhanced focus on neurological disorders aligns well with these subgoals. The overall agenda of the SDGs paves way for a strong focus on equity, requiring fair resource distributions within and between countries and emphasizes the importance of universal health coverage (UHC), defined as "*ensuring that all people have access to needed health services that all people obtain the health services (including prevention, promotion, treatment, rehabilitation and palliation) of sufficient quality to be effective while also ensuring that the use of these services does not expose the user the financial hardship"* [19]. Because of the high prevalence, focusing on neurological diseases is necessary to yield effective UHC. Furthermore, the Covid-19 pandemic underlined the need for more sustainable, long-term solutions for global health issues and highlighted strengths, vulnerabilities, and inequalities of health systems. Disease prevention, health promotion, a more efficient use of resources as well as a global focus on health equity are all factors neurological disorders can benefit from.

1.3 The complexity of neurological disorders management in Sub-Saharan Africa

It is expected that the burden of neurological disorders will increase more in low-income countries (LICs) than in richer regions [3, 4]. As mentioned in Section 1.1, the global prevalence of dementia is expected to increase by 219% in 2050 [17], but for LICs the increase is projected at 264% [17, 20]. Also the majority (65%) of the economic burden will be placed on low- and middle-income countries (LMICs) [21]. One of the causes of this prevalence increase is the demographic transition. Considering Sub-Saharan Africa, the life expectancy at birth has increased [8], and aging is deemed as a risk factor for developing a neurodegenerative disorder [22], resulting in an increased prevalence in this region. A second factor is the double burden of disease, that combines the burden of CDs with NCDs [23]. For example, infectious outbreaks, for example HIV, malaria, or parasitic diseases such as onchocerciasis (CDs), have resulted in an increase in chronic epilepsy cases (NCDs) [24]. Furthermore, several infectious neurological diseases in Sub-Saharan Africa are preventable, such as tetanus and meningitis[3, 4]. Yet, the increase of the prevalence of infectious neurological disorders will inevitably result in a higher disease burden, but also a higher

economic burden [4, 14, 25], both from direct costs as well as the indirect costs associated with these diseases.

Stroke and head injury are already among the leading causes of death caused by neurological diseases in hospitals in Sub-Saharan Africa [26], and among the most common causes of disability are stroke, head trauma, and epilepsy [27]. The consequences of the burden of neurological disorders extend from physical to cognitive and often pose many other psychosocial challenges [25]. In Sub-Saharan Africa, patients with neurological disorders regularly experience stigma or discrimination, often due to a lack of understanding or unfamiliarity with the disorder, or because the disorder is perceived as the effects of witchcraft or possession [24]. Stigma is defined as *"the way in which societies relate to a person or a group of persons who is/are in some way different or possesses certain attributes that the society considers to be discrediting"* [28]. Consequentially, this stigmatization affects the whole family, as patients could be denied access to health services or even exclusion from society [29].

Furthermore, human resources are lacking for appropriate neurological care, as the ratio of neurologists to people is extremely low in Sub-Saharan Africa [30]. Therefore it is more accessible for patients to seek council from a natural healer instead, which could lead to a lack of recognition of a disorder (underdiagnosis), and miss out on possible effective treatment- or disease-management options [31]. Even when patients have access to a specialist, treatment options are often limited due to a lack of resources, forcing patients to turn to expensive private clinics [27, 31]. UN's International Covenant on Economic, Social and Cultural Rights states that access to health care is a human right [32]. This covenant poses an obligation of state conduct, to provide acceptable health care services, including focus on the social determinants of health *[33]*. Altogether, scaling-up of neurological care is needed, however, there still is a long way to go.

Given the complexity of neurological disorders in Sub-Saharan Africa, for this thesis it was chosen to focus on three East African countries, namely Ethiopia, Malawi, and the United Republic of Tanzania (from now on referred to as Tanzania). These countries were selected as they are close in distance, but different in terms of culture, religion, politics, and economy. In addition, a close working relationship was already established between BCEPS and two of the three settings. I will next introduce the three settings in terms of characteristics and key health challenges.

1.3.1 Ethiopia

Ethiopia has gone through many political changes in a short time span, and multiple conflicts of different origins that have affected the political, economic, and cultural situation. The economy has been growing with 9.4% since the last decade, yet is slowing down as a result of civil war and the Covid-19 pandemic [34]. Ethiopia is densely populated with around 112 million people in 2019, and a population growth of around 2.6% per year. Since 1990, the average life expectancy of Ethiopians has increased with 10 years and now lies at 66.6 years at birth in 2019 [34]. Ethiopia had a GDP per capita of US$944 in 2021 and is classified as a LIC (i.e., GDP per capita under US$1035) [35]. In 2015, it was estimated that around 23.5% of the population lived below the national poverty line [36]. Throughout the years, health reforms have led to health services gradually becoming more available over time, with more HR personnel, health centers and health posts, with UHC of 34.3% in 2015 (ranging between 52.5% in the capital Addis Ababa to 10% in the rural Afar region) [37]. Despite the progress, UHC is still low, and scarcity of resources, funding, health staff and access to appropriate care are still a challenge. Additionally, how the consequences of the current conflict and the ongoing pandemic might further influence the country and affect the most vulnerable in society regarding health services in the future remains unknown.

1.3.2 United Republic of Tanzania

In 2020, The United Republic of Tanzania (referred to as Tanzania) moved status from LIC to LMIC, as a result of a stable economy with over 6% economic growth in the last 10 years, due to agriculture, mining and tourism. Simultaneously, the population is increasing at annual rate around 3%. The population of Tanzania was estimated at 61 million people in 2021. Despite the steady economic growth of Tanzania, the population growth is likely to further increase the levels of poverty and inequality [38]. Tanzania had a GDP of US$1135.5 in 2021. In 2018 26.4% of the population lived below the national poverty line [36].

Tanzania has focused on efforts on keeping health care equitable and accessible to all. For example, the semi-autonomous region of Zanzibar has made an effort to make health services free for over half a century. However, in practice, funding and resources are lacking, such as medical supplies, medicine, and trained staff, forcing patients to resort to private clinics, often with catastrophic out-of-pocket expenditures.

1.3.3 Malawi

Malawi is classified as LIC with a GDP per capita of US$642.7 in 2021, making Malawi one of the poorest countries in the world. In 2016 about half the population were below the national poverty line [39]. Malawi has made efforts in order to improve structural economic growth, resulting in a 4.8% economic growth prior to the Covid-19 pandemic. However, the impact of Covid-19 is vast, resulting in an increase in poverty [40]. Still, the recent Malawi 2063 Vision policy directs towards a rebound of the economic growth and improving efforts in order to reach upper middle-income country status [41]. In 2019, Malawi was home to 18.6 million people, of which almost 80% were working in agriculture [40]. The population is expected to double before 2040 and has a growth rate of 2.65% [39].The life expectancy is 63.7 years at birth [40].

Health care accessibility in Malawi is challenging. For the population that lives in remote areas, getting access to timely health care is difficult due to the long distances. Furthermore, services are fragmented, staff are lacking, and the double burden of disease is high. It is estimated that Malawi has 0.019 medical doctors and 0.283 nurses per 1000 people, which comes down to less than 600 medical doctors for the whole population [42]. It is estimated that in tertiary hospitals in Malawi around 70% of care is provided for diseases and conditions that on paper should be treated in lower-level health care facilities. The essential health care package has been expanded to include treatment of some non-communicable diseases, but service delivery should be improved in order to reach a decent level of available and acceptable care [43].

2. Rationale, objectives and hypotheses

2.1 The rationale for a cost-effectiveness analysis on neurological interventions in priority setting

The burden of neurological disorders will increase in countries like Ethiopia, Malawi and Tanzania, but their health systems are currently not well equipped to manage this increased burden [31]. Additional problems extend to conflict, corruption, mistrust, and a lack of accountability and transparency of governmental institutions that affect effective health care delivery. More needs to be done in order to diminish inequalities caused by neurological disorders, to reflect upon the implications of the current policy and to improve the management of neurological disorders and scale up interventions in areas that are resource deprived [31]. A cost-effectiveness analysis can provide further insight in efficient resource allocation and aid policy makers on this topic.

After consultation with the neurological experts that co-author on the paper (Appendix I), it became clear that in the selected settings, neurological interventions receive limited to no treatment. These disorders are not included in UHC, so treatment relies on out-of-pocket (OOP) expenditures. Consequentially, treatment cannot be afforded by many, and health expenditures can push people into poverty. This creates a dire vicious cycle, as poverty is a predictor of ill health, but ill health also contributes to (deeper) poverty because of high OOP-expenditures. This can eventually result in a barrier for accessible health care, making treatment options or prevention measures a financial risk, essentially widening the already existing treatment gap. The first goal of UHC is to bridge these barriers in health care services by creating accessible and available health care without the risk of impoverishment. Thus, UHC decreases disparities and increases financial risk protection by reducing the OOP-expenditures. Secondly, expanding UCH includes a broader population and carefully and ethically selects disease priorities [44, 45]. A health economic evaluation can be seen as a basic facilitation tool to deliver evidence for revision of the current UCH package. Health economic evaluations provide evidence on which interventions are best-buys, information that can guide health policy and aid priority setting [46].

Furthermore, the current evidence on the cost-effectiveness of neurological interventions in LLMIC settings is thin, despite the projected increase in prevalence of neurological disorders. Therefore, the main aim of this thesis is to conduct a cost-effectiveness analysis (CEA) for epilepsy, migraine, dementia, and Parkinson's disease in Ethiopia, Malawi, and Tanzania. The analyses were performed using the FairChoices – DCP Analytics Tool (FairChoices) [47], which has been developed at BCEPS [48].

2.2 The rationale behind the disorder and intervention selection

As it is not feasible to include all neurological disorders, this thesis will take further direction zooming in on migraine, epilepsy, Parkinson's disease, and Alzheimer's disease and other dementias (referred to as "Dementia"; Table 1), based upon the GBD cause list [49]. An elaborate background of these disorders and interventions, considerations for the model, along with the input parameters used in the model can be found in Appendix 2 "Evidence briefs".

The neurological interventions per disorder were selected based on the available prevention and treatment options for two delivery platforms: district/regional hospitals, or in the community (Table 1). The interventions were selected from a list of recommendations from Disease Control Priorities 3 (DCP3) [25]. Additional interventions (e.g., the various drug treatments of dementia) are not on this list but were added to create a more complete

overview for the disorders and potential treatment options. Including these interventions might seem counterintuitive at first, due to the high costs associated with drug treatment, for example because of the lack of accessibility of pharmacological options for dementia. Cost-effectiveness analyses are relative in characteristics, depending on a myriad of factors in a specific context, among which, a countries willingness to pay, and because of this, interventions might become relevant at a later time point. The availability of information on these interventions can thus be very informative for decision makers later on during future essential health package revisions, to reduce the treatment gap, and to explore possibilities to manage the various disorders if scaling up interventions becomes a possibility.

Table 1: Disorders and intervention characteristics

Disorder	Type of intervention	Delivery platform	Description of the intervention
Epilepsy			
▪ Acute stabilization	Curative/ management	Hospital	Basic psychosocial support, advice, and follow-up, plus anti-epileptic medication (20 mg diazepam + 100 mg phenobarbital)
▪ Long-term management with generic anti-epileptics	Curative/ management	Hospital	Basic psychosocial support, advice, and follow-up, plus anti-epileptic medication (100 mg phenobarbital)
Migraine			
▪ Self-managed treatment	Curative / management	Community	Basic psychosocial support, advice and follow-up, plus first-line pharmacological treatment
▪ Preventative and self-managed treatment	Curative / management	Community	Basic psychosocial support, advice and follow-up, plus first-line pharmacological treatment including prophylaxis
Dementia			
▪ Drug treatment: Cholinesterase inhibitors	Curative/management	Hospital	Pharmacological treatment of dementia, advice and follow-up
▪ **Drug treatment:** SSRIs	Curative/management	Hospital	Pharmacological treatment of dementia, advice and follow-up
▪ Supporting dementia caregivers	Promotion	Community	Interventions focused on training, educating and support caregivers of dementia patients
Parkinson's disease			

• Long term management with drug treatment	Curative/management	Hospital	Drug treatment with levodopa/carbidopa, advice, psychosocial support and follow up for mild, moderate and severe phases of the disorder.
▪ Physical therapy	Curative/management	Hospital	Basic physical therapy (6 sessions a year)

In the initial phase, stroke was considered for the paper and thesis due to its high mortality. However, as stroke is categorized under cardiovascular diseases in the GBD cause list, it was excluded from this analysis. Other neurological disorders, like amyotrophic lateral sclerosis (more known as ALS) or multiple sclerosis were excluded due to a lack of treatment options.

Additionally, diagnosis and follow up care was a separate intervention for each of the disorders. However, as diagnosis is a requirement for treatment, with limited health effect by itself, it was decided to include only the costs for diagnosis into the existing interventions. This was done by estimating the diagnosis costs, dividing these by 10 years and included this amount into the annual unit costs per intervention.

The evidence brief on dementia provides cost and effectiveness information on antipsychotics, however, it was decided to exclude antipsychotic drugs from the analysis. Despite that these drugs are still widely used to treat behavioral and psychological symptoms (such as agitation), antipsychotics are not recommended because of their significant side effects and small effect size, and should only be used when patients fail to respond to other forms of pharmacological treatment.

In the evidence brief on Parkinson's disease information was added on two interventions, namely surgery, and 2 sessions of basic physical therapy, but were later excluded. Surgery was excluded as there are currently no neurosurgeons available in Malawi that perform this surgery, and no comparative information could be found on costs in similar settings. For physical therapy, two different intensities were considered before settling on six sessions per year, as two sessions might be more feasible than six sessions, but this frequency was too low and was omitted.

2.2 The aim and objectives of the current health economic evaluation

The current evidence on the cost-effectiveness of neurological interventions in LLMIC settings is thin, despite the projected increase in prevalence of neurological disorders. Therefore, the main aim of this thesis is to conduct a cost-effectiveness analysis (CEA) for epilepsy, migraine, dementia, and Parkinson's disease in Ethiopia, Malawi, and Tanzania.

Specifically, the objective for the paper is to estimate the ICERs of the nine neurological interventions listed in Table 1, for four neurological disorders (epilepsy, migraine, dementia and Parkinson's disease) for a 10-year time period, and to compare the results in three East African settings (Ethiopia, Malawi, and Tanzania) for a scale-up from baseline coverage of 10 percentage points (pp), in order to provide evidence that could support health policy makers in making educated decisions on the improvement of health care systems.

The analyses were performed using FairChoices [44], which has been developed at BCEPS [45]. The main measure of cost-effectiveness is the incremental cost-effectiveness ratio (ICER), which is calculated by dividing the difference in costs with the difference in effectiveness of two interventions [46]. Since coverage of neurological interventions is very low in Ethiopia, Malawi, and Tanzania, the comparator is "no intervention" (i.e., 0 cost and 0 gain). Hence, the reported ICER for an intervention is simply its cost, measured in $US, divided by its effect, measured in healthy life years (HLYs) gained.

HLYs gained are similar to the better-known concept of DALYs averted. DALYs are used as a measure of disease burden, whereas HLYs are a measure of the number of years a person is expected to continue live a healthy life [50]. A DALY is a measure of the years lived with disability (YLD), that includes various disability weights for different diseases, combined with the years of life lost (YLL), as a result of dying earlier than the life expectancy would be for a person with the same age [46, 51]. HLYs gained, however, are calculated by taking the healthy life expectancy of a person that has been given a certain intervention, and subtracting the healthy life expectancy that person would have without the intervention. Healthy life expectancy data includes average experienced (sex- and age-specific) disability weights. For a patient with a neurological disorder, the disability weight is the sum of all disability (from all other causes) and the disease-specific disability. The difference in effect is determined by evidence of the disability- or mortality reduction of the interventions that was gathered through literature reviews, prioritizing evidence gained through literature reviews or meta-analyses. In order to calculate the budget impact, the cost of an intervention is split into drug prices and HR costs. HR costs are calculated based on salaries and the time a health worker spends with a patient with a specific neurological condition. This thesis has a health care provider perspective, therefore costs from a patient point of view (such as out of pocket expenditures or health insurance), or recurrent costs such as building costs or electricity are excluded. The main results focus on a 10 pp scale-up of each intervention, but because costs and effect are assumed to increase linearly when scaling up coverage, the costs and health

gains for other scale-ups can be calculated directly from the results from the 10 pp scale-up. For example, both costs and effects for a scale-up of 40 pp are four times higher than the for the 10 pp scale-up. ICERs are not impacted by the scale-up.

The previous sections provided background information on the current status of neurological disorders and the settings, that can support understanding of the relevance of the paper. Prior to moving on to the next section, I recommend reading the paper in appendix 1 first.

3. Methods and methodological considerations

The paper already provided an elaborate methodology section of the cost-effectiveness analysis, and in this current section, the rationale, justification, strengths and limitations behind the methodology are provided.

Considerations concerning risks and benefits of the chosen methodology

Data modeling provides many advantages over using traditional randomized clinical trials, the biggest advantage being the increased opportunity of synthesizing data that can be tough to obtain otherwise, and omits ethical conflict as data are hypothetical as they are simulated. Because of these strengths, FairChoices [47] was used to determine the cost-effectiveness of the selected interventions (for a glance of this tool, see Appendix 3). FairChoices uses a determinist approach to conduct CEA.

The biggest risk with modelling versus randomized trials is that any errors in input automatically equal incorrect output. This was particularly challenging as in the selected settings, some data were not available so analyses would rely on data from high income countries, or sometimes an initial educated guess. To reduce the risk of errors, and to increase validity and reliability, the cost and effectiveness data was discussed internally within the research group, as well as verified with a group of neurologists from the respective countries. I personally feel that verifying the data with both health economics, statisticians and neurologists in these East African settings has made the study a lot more trustworthy. Despite this strength, from my perspective. Still, the input always reflects an approximation of the true values. Furthermore, underdiagnosis and lack of treatment options might give a skewed image of prevalence and incidence, and lack of availability of interventions or drugs provides challenges in costing. However, the information used is the best available information, which highlights the need for further research.

As alternatives to the deterministic model in FairChoices, a decision tree approach and a Markov approach were considered. The advantage of a decision tree is that it provides a

simple, yet intuitive overview of the data, taking into consideration the possibilities of events occurring, that can easily determine the best outcome in a given situation. However, given the complexity of the interventions (e.g., multiple disease stages of drug treatment or subgroup analysis for migraine prophylaxis), the model would no longer be intuitive. A Markov model was considered to be a good alternative as this includes a timing component of serial events, in which a group of modelled patients move through a disease cycle with several phases until an absorbing state has been reached [46]. This could be useful when patients diagnosed with Parkinson's disease or migraine move from the first-line treatment to a second-line treatment in case the first-line treatment may not suffice anymore. However, a Markov model was not fully applicable to all of the selected interventions. To evaluate the uncertainty of the input, a one-way sensitivity analysis was conducted (Appendix 1). This was a necessity given the amount of uncertainty the data input contained in order to factor in uncertainty in their outcomes. As an example, some costs (like some costs for dementia- or Parkinson's drugs) could not be obtained in the right settings and I had to derive the information from other, non-African settings.

Considerations and justifications on the analysis

Initially, the idea was to include Zanzibar as a separate region as well. I decided however to focus on the United Republic of Tanzania as a whole, as the HR costs for some occupations were unavailable, or the HR costs that were obtained did not differ from the costs from mainland Tanzania. Therefore, as the unit costs were the same, so was the output.

Secondly, we wanted to compare intervention packages by creating a package for each disorder with the selected interventions. This idea was abandoned after the many subgroups that complicated the analysis. For example, only a subgroup of migraine patients benefit from prophylaxis, and not all epilepsy patients need acute stabilization, and drug treatment varies between the different disease stages of Parkinson's disease. Therefore it was decided to simplify each intervention instead.

Lastly, the aim was to identify interventions as best-buys. To do so we considered using the net health benefit approach [52] to determine cost-effectiveness thresholds, as well as the 1x-3x GDP per capita approach [53]. However, the first approach is beyond the scope of this master thesis, and the second is outdated. In addition, using other cut-offs for cost-effectiveness (like US$100/HLY gained or US$500/HLY gained) were arbitrary, as the willingness to pay for a country determines the threshold.

Future considerations

Furthermore, one of the future steps will be to include non-health outcomes such as financial risk protection and a broader equity perspective in a follow-up study, by carrying out an extensive cost-effectiveness analysis. However, because of time constrains and resource limitations, as well as the project scope, adding this additional research is not feasible for one master's thesis. Still, it is important to acknowledge that there are non-health benefits that can be gained that can affect the individual, their direct network or society, in a prospective revision of health care packages. Therefore, improvement made on (a combination of) these non-health factors can gradually contribute to increased equity. This includes cost implications, extending from an individual perspective to a family or society perspective as a direct result from increased productivity or school performance of the individual, but also informal caregivers. Other non-health outcomes improve the quality of life, increased social participation, stress reduction, but also broadens to ease the workload on the health care system, that can result into more accessible and acceptable care.

Conclusion

In this thesis, evidence is provided on the cost-effectiveness of scaling-up neurological interventions for epilepsy, migraine, dementia, and Parkinson's disease in Ethiopia, Malawi, and Tanzania. In the paper, throughout the three settings, the following six interventions were the most cost-effective: acute stabilization and long-term management for epilepsy, for migraine this includes both treatment with ASA and ASA+ prophylaxis, caregivers of dementia patients and physical therapy for Parkinson's disease patients. Drug treatment for dementia and Parkinson's disease had a high budget impact and lower health benefits. These results are comparable with findings from other studies. Overall across the three settings, the budget impact and the health gains were the highest in Ethiopia, and the lowest in Malawi, with the lowest ICERs identified in Tanzania. The difference between the countries can be attributed to differences in terms of HR-costs and disease prevalence. Whether these results are deemed cost-effective is decided by the willingness to pay in the three settings.

Further research is needed in order to gain more evidence on (other) neurological disorders in LLMIC settings. The prevalence of dementia is projected to increase the most, particularly in LLMIC settings, and in this cost-effectiveness it has the biggest budget impact. Therefore, it is recommended to focus on additional (cost-effectiveness) research including non-health benefits that can be gained from the current and other interventions.

In conclusion, the expected increase in the burden of neurological diseases can be lessened if interventions are scaled up. Drug treatment of epilepsy and migraine and non-drug

treatment of PD and dementia would give the most benefit per dollar spent. Focusing on efficient management of neurological disorders therefore can make a vast impact on the current and future disease burden on a global scale.

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Appendix 1. Paper and supplementary file

Essential neurological interventions in East Africa: a health economic evaluation

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Abstract

Introduction: Neurological disorders causes considerable disease burden globally, both measured as deaths and disabilities. A vast increase in disease burden is projected in near future in low- and lower middle-income countries (LLMIC). Despite effective interventions being available, neurological disorders are often neglected, underdiagnosed, receive insufficient funding, and research is limited. The objective of this paper is to assess cost-effectiveness of essential neurological interventions in Ethiopia, Malawi and Tanzania that currently have low effective coverage levels.

Methods: This is a health economic evaluation of interventions targeting epilepsy (acute- and long-term management), migraine (ASA and prophylaxis), Parkinson's disease (drug treatment, physical therapy), and dementia (drug treatment, interventions targeting caregivers) to inform policy makers in Ethiopia, Malawi, and Tanzania. Health system costs were collected through a top-down micro-costing method. Costing and coverage data were collected with the expertise of East African neurologists and medical experts. Efficacy estimates were gathered by estimating the mortality or disability reduction, based on meta-analyses or systematic reviews. The cost-effectiveness analyses, calculating the incremental cost-effectiveness ratio (ICER), were conducted with *FairChoices: DCP Analytics Tool*. The health benefits of the interventions were estimated in healthy life years gained (HLYs).

Results: six interventions were identified as cost-effective in all three settings: Parkinson's disease: basic physical therapy (range of ICERs between the three settings: US$138 to 187 per HLY); epilepsy: long-term management (8 to 16 US$ per HLY), acute stabilization (109 to 174 US$ per HLY); dementia: caregivers of dementia patients (28 to 94 US$ per HLY), Migraine: ASA (146 to 234 US$ per HLY) and ASA+ prophylaxis (136 to 338 US$ per HLY).

Conclusion: The current findings support that an impact in managing neurological conditions can be made by scaling-up the identified cost-effective interventions in resource-constrained settings. By including these considerations carefully, a revision of the essential health benefit package can initiate a prime step forward in pursuit of poverty reduction and health equity.

Keywords: cost-effectiveness analysis, epilepsy, migraine, dementia, Parkinson's disease, Eastern Africa, Malawi, Tanzania, Ethiopia.

Introduction

Worldwide, more than 2.5 billion people suffer from neurological disorders, with about 800 million new cases each year [54]. Without adequate management of neurological disorders, the already high mortality (2.2 million deaths worldwide in 2019) and morbidity (98 million disability adjusted life years (DALYs) worldwide in 2019 [54]) levels have been predicted to increase drastically in near future, and an even steeper increase is expected within the upcoming generation on a global scale [14]. Because of demographic and epidemiological transitions, the increase in the incidence of non-communicable neurological disorders is expected to be particularly steep in low- and lower middle-income countries (LLMIC), while the share of communicable neurological disorders (i.e. tetanus, meningitis and encephalitis) is expected to further decline [3, 4, 55, 56]. Over the last decades, health services in the East Africa region have undergone vast improvements [57-60], but despite universal political commitments on achieving universal health coverage (UHC) in alignment with Sustainable Development Goal target 3.8[18], a myriad of political, economic, and cultural circumstances hinder further progress [57].

To get one step closer towards including neurological interventions into UHC in East Africa, cost-effectiveness data of neurological interventions can be used to aid national health priority setting by informing policy makers on the allocation of limited resources [6, 14]. The available evidence on cost-effective neurological interventions for high income countries has limited relevance in East African settings, and the existing evidence for neurological interventions in this setting appears to be limited . A study that was carried out in China, Russia, India, and Zambia found that acetylsalysilic acid (ASA) was the most cost-effective treatment for acute migraine attacks, and identified that amitryptiline was the most cost-effective prophylactic option [61]. We found little further evidence for cost-effectiveness analysis of other neurological interventions conducted in African settings.

A study from 2012 found that phenobarbital used to treat epileptic seizures was highly cost-effective in the Eastern Sub-Saharan Africa region [62, 63]. This was confirmed in a study from 2016 showing that the newer drug carbamazepine was less cost-effective than phenobarbital in Ethiopia [64]. For other neurological disorders like dementia or Parkinson's disease, we have not been able to find cost-effectiveness analyses in LLMIC settings. It has even proved challenging to estimate the prevalence of these disorders [65].

In East Africa, neurological disorders are often underdiagnosed, carry stigma, specialized health care workers are lacking, and treatments are underfinanced [29, 31]. Access to health care in public health settings for neurological conditions is limited, in part because of a scarcity of resources like medicine, staff, and money [7, 31]. As a step towards UHC, LLMICs typically offer publicly financed essential health care packages that include top priorities and cost-effective interventions to prevent, cure, or promote health.

By obtaining more insight into the cost-effective interventions, neurological conditions can be better managed or even prevented in research constrained settings. Therefore, the aim of this study is to facilitate better management of neurological interventions in Malawi, Tanzania, and Ethiopia, by carrying out a cost-effectiveness analysis targeting epilepsy, migraine, dementia, and Parkinson's disease.

Methods

In this health economic evaluation cost and effectiveness were estimated from a health provider perspective. Ethiopia and Malawi are low-income countries, whereas the United Republic of Tanzania (referred to as Tanzania) is a lower middle-income country, allowing for a comparison of the cost-effectiveness between settings.

Interventions

The interventions included in this cost-effectiveness analysis targeted epilepsy, migraine, Parkinson's disease, and dementia (Box 1). Interventions targeting neurological disorders with a cardiovascular or infectious origin, such as stroke or meningitis, were excluded, as well as those targeting other neurological disorders without effective treatment options (such as ALS or Huntington's disease). Table 1 shows the prevalence, incidence, mortality, and DALYs caused by the selected disorders in the different settings. For each condition, multiple interventions were selected based on the curative, preventive, or promotional characteristics of the treatments available.

The treatments of the different conditions were divided into categories as follows: epilepsy: acute stabilization (10mg diazepam + 100mg phenobarbital) and long-term management (100mg phenobarbital); migraine: first-line medication (ASA) to treat acute attacks and prophylaxis to prevent attacks from happening; dementia: drug treatment (cholinesterase inhibitors and SSRIs), and caregivers of dementia patients; and Parkinson's disease: drug treatment, and basic physical therapy). For cholinesterase inhibitors we assessed the effects of donepezil, rivastigmine and galantamine. Fluoxetide was selected as SSRI of choice due to its availability in East Africa to treat behavioral and psychological symptoms of dementia. Parkinson's disease was split up in 3 disease stages based on years since diagnosis (mild: 0-5 years, moderate: 6-9 years, severe: >10 years), because medication effectiveness wears off over time requiring a higher dosage. For Parkinson's disease, basic physical therapy was defined as 6 sessions per year of 30 minutes.

Box 1: an overview of the interventions

Epilepsy treatment
Stabilization of acute seizures
Long-term management of epilepsy
Self-managed treatment of migraine
Basic psychosocial support, advice, and follow-up, plus first-line medication (ASA)
Basic psychosocial support, advice, and follow-up, plus first-line medication (ASA) & prophylaxis
Dementia care
Drugs for dementia - cholinesterase inhibitors
Drugs for dementia - SSRIs
Supporting dementia caregivers
Parkinson's disease
Drugs for Parkinson's disease (mild phase)
Drugs for Parkinson's disease (moderate phase)
Drugs for Parkinson's disease (severe phase)
Basic physical therapy for Parkinson's patients

The interventions targeting epilepsy, migraine and Parkinson's disease are aimed at all prevalent cases, whereas for dementia, one intervention targets caregivers of a family member diagnosed with dementia. All interventions are compared to a null scenario where no treatment is provided.

Data sources

For each intervention, a literature review was conducted, providing evidence regarding cost and efficacy. In addition to the general literature, sources included the Ministries of Health in Tanzania, Ethiopia and Malawi [58-60, 66, 67]. For the conditions targeted by the interventions, age-specific estimates on prevalence and incidence, mortality, and disability were available from the Global Burden of Diseases and Injuries (GBD) study [3, 4, 12, 68, 69] more, four neurologists and two medical professionals from the three countries were involved and provided estimates of human resources (HR) time per patient, effectiveness, baseline coverage, and costing information to obtain a realistic, feasible scenarios for diagnosis and treatment.

Table 1: epidemiology and baseline characteristics

Condition	Country	Prevalence (rate)	Incidence (rate)	Mortality (rate)	DALYs (absolute, thousands)
Idiopathic Epilepsy	*Eastern SSA region*	366.20	51.39	1.67	979
	Ethiopia	276.85	45.33	1.48	204
	Malawi	345.03	46.92	1.78	44
	*Tanzania**	380.28	44.65	1.70	137
Migraine	*Eastern SSA region*	7 865.78	794.12	n/a	1 221
	Ethiopia	7 165.69	738.40	n/a	286
	Malawi	8 054.97	830.90	n/a	56
	*Tanzania**	8 117.42	808.00	n/a	175
Alzheimer's and other dementia's	*Eastern SSA region*	150.44	22.48	5.20	354
	Ethiopia	156.43	23.58	5.98	103
	Malawi	157.63	23.44	5.53	16
	*Tanzania**	175.77	25.73	6.42	58
Parkinson's Disease	*Eastern SSA region*	18.90	2.59	1.12	86
	Ethiopia	18.96	2.51	1.14	22
	Malawi	19.35	2.75	1.16	4
	*Tanzania**	21.09	2.92	1.33	14

* Official name: United Republic of Tanzania; SSA: Sub-Saharan Africa
All data are obtained from the GBD Results Tool (https://ghdx.healthdata.org/gbd-results-tool [54])

Effectiveness assumptions

The input parameters for effectiveness of the interventions are based on evidence on reduction of prevalence, incidence, disability, or mortality from RCTs, literature reviews, and meta-analyses from the Cochrane and PubMed databases (Table 2). The disability weights per condition [70] were included to calculate the change interventions have on the number of healthy life years gained (HLYs) (Table 2). For cholinesterase inhibitors and SSRIs, the effectiveness was not reported as a reduction in prevalence, incidence, disability, or mortality, so reported effects were converted to correspond to a change in disability weight. In the case of Parkinson's disease drug treatment, the effectiveness was assumed per disease stage (mild, moderate, severe) and estimated by two independent neurologists. The effectiveness of the physical therapy interventions was estimated by a physical therapist specialized in Parkinson's disease. The "affected fraction" column in Table 2 was used for the Parkinson interventions as well as acute stabilization of epilepsy, where only a subgroup of prevalent cases benefit from the interventions. An average disability weight was calculated for all Parkinson's and dementia patients in East Africa by dividing GBD estimates for years lived with disability (YLDs) by the prevalence[54].

The effectiveness of the cholinesterase inhibitors and SSRIs were estimated by determining the level of cognitive decline over time in comparison to a placebo on a cognitive screening test, the Mini Mental State Exam (MMSE) [71], and calculating a disability-weight-per-point difference. The interpretation of the MMSE indicates that a score between 25-30 points equals no indication for cognitive decline, whereas a score of <9 points is indicative for severe cognitive decline. Given the disability weights of 0 for no cognitive decline, and 0.449 for severe cognitive decline (see Table 2), it was assumed that these disability weights correspond to the different point ranges, yielding a- change per point: 0.449/(25-9) = 0.028 ,

Hence, if the total MMSE score increases by 1, the disability weight will drop by 0.028. To estimate the efficacy of an intervention, the increase in MMSE associated with the interventions is multiplied by 0.028, and then this number is divided by the average disability weight (i.e., 0.14) for dementia in the Eastern Sub-Saharan Africa region in GBD (i.e., total YLDs for dementia divided by absolute prevalence of dementia) [54]. For example, if MMSE increases by 0.9 when using cholinesterase inhibitors, this translates into a 0.9*0.028=0.0252 drop in the dementia-specific disability (i.e., 0.0252/0.14*100%=18%). Lastly, as the dementia caregivers intervention carries no clear health benefit, the input parameters for effectiveness were deliberately kept low. The disability weights [70] for all conditions can be found in Table 2.

Table 2: effectiveness parameters per intervention

Condition	Treatment option	Effectiveness (sensitivity interval*)	Disability weight	Affected fraction	Uncertainty factor (%)	Source
Epilepsy	Diazepam + Phenobarbital	Mortality reduction: 1 Affected fraction: 0.4 (0.29 - 0.56)	Severe: 0.552 Less severe: 0.263	0.4	25	[64, 72-76]
	Phenobarbital	Mortality reduction: 1 (0.64 - 1) Disability reduction: 0.8 (0.64 - 1)	Severe: 0.552 Less severe: 0.263	1	25	[64, 72-76]
Migraine	Aspirin	Disability reduction: 0.39 (0.31 - 0.49)	0.441	1	25	[77]
	ASA + prophylaxis	Disability reduction: 0.63 (0.47 - 0.84)	0.441	1	33,33	[61, 77]
Dementia	Donepezil Galantamine Rivastigmine	Average disability reduction: 0.2 (0.13 - 0.3)	Mild: 0.069 Moderate: 0.377 Severe: 0.449	1	50	[78, 79]

	Fluoxetide	Disability reduction: 0.2 (0.13 - 0.3)		1	50	[80]
	Caregiver interventions	0.1 - limited direct health benefits assumed	n/a	1	50	
Parkinson's disease	Levodopa/ carbidopa	Disability reduction: 0.8 (0.64 - 1) Disability reduction: 0.3 (0.21 - 0.42) Disability reduction: 0.08 (0.05 - 0.12)	Mild: 0.010 Moderate: 0.267 Severe: 0.575	0.36 0.35 0.29	25 40 50	[81]
	Physical therapy (basic)	Disability reduction: 0.3 (0.27 - 0.375)	Mild: 0.010 Moderate: 0.267 Severe: 0.575	1	25	[82]

Mortality reduction: 0 means no effect, 1 means 100% effective in preventing death
Disability reduction: 0 means no effect, 1 means 100% effective in reducing disease-specific disability
Sensitivity intervals were calculated by increasing and decreasing costs and effects by an uncertainty factor (see *Data analysis*)
Affected fraction indicates the (sub)group that benefits from the intervention, 1 means 100% of the affected population benefit

Cost assumptions

Costs were collected for drug prices, salaries for health care workers, material costs, and other miscellaneous costs like diagnosis for treatment in the settings in Ethiopia (collected by co-authors SAG, AMB, STM, and MTT), Malawi (collected by co-author TEKP), and Tanzania (collected by co-authors KOM and OMO). Costing data were collected between August 2020 and June 2021, in local currency, and converted to US dollars with the 2021 exchange rate for June 2021, so that one US$ equals 0.012 Malawi Kwacha, 0.0229 Ethiopian Birr and 0.00043 Tanzanian Shilling. For each intervention, country-specific annual unit costs were calculated. Costing parameters can be found in Table 3. Costs for diagnostics based on clinical assessment only were calculated from HR-costs per patient and divided by the intervention period duration (10 years) and added to each separate intervention. In Ethiopia, Malawi, and Tanzania, neuroimaging and specific tests to support diagnosis are not widely available, or lack validation, so for these reasons, these costs were not included in the diagnosis costs. Further, as a health provider perspective was used, other costs, such as indirect expenses caused by work absenteeism, or costs for infrastructure or travel were not included.

Table 3: costing parameters per country/region per intervention

Country	Condition	Treatment	HR-costs per case (US$)	Drug price per year US$ (average case)	Diagnosis cost (US$)	Cost uncertainty factor (%)	Unit costs (US$)
Ethiopia	Epilepsy	Acute stabilization (diazepam + phenobarbital)	6.07	1.95	0.18	33.33	8.20
		Long-term management (phenobarbital)	3.05	1.94	0.18	20	5.17
(GDP per capita: US$ 944 in 2021)	Migraine	First-line analgesics (ASA)	1.86	0.22	0.18	20	2.26
		First-line analgesics (ASA) + prophylaxis	1.86	3.24	0.18	33.33	5.28
	Dementia	Cholinesterase inhibitors	3.55	620.50	0.18	50	624.23
		SSRIs	3.55	3.50	0.18	33.33	7.23
		Caregivers of dementia patients	0.62	n/a	0.18	20	0.80
	Parkinson's disease	Drug treatment: Mild	3.55	69.75	0.18	50	73.48
		Moderate	3.55	109.61	0.18	50	113.34
		Severe	3.55	159.43	0.18	50	163.16
		Basic physical therapy	5.18	n/a	0.18	25	5.36
Malawi	Epilepsy	Acute stabilization (diazepam + phenobarbital)	6.54	1.95	0.19	33.33	8.68
(GDP per capita: US$ 642.7 in 2021)		Long-term management (phenobarbital)	3.29	1.94	0.19	20	5.42
	Migraine	First-line analgesics (ASA)	1.79	0.22	0.19	20	2.20
		First-line analgesics (ASA) + prophylaxis	1.79	3.24	0.19	33.33	5.22
	Dementia	Cholinesterase inhibitors	3.76	620.50	0.19	50	624.45
		SSRIs	3.76	3.50	0.19	33,33	7.46
		Caregivers of dementia patients	0.24	n/a	0.19	20	0.43
	Parkinson's disease	Drug treatment: Mild	3.76	69.75	0.19	50	73.70
		Moderate	3.76	109.61	0.19	50	113.56
		Severe	3.76	159.43	0.19	50	163.38
		Basic physical therapy	5.94	n/a	0.19	25	6.13
Tanzania	Epilepsy	Acute stabilization (diazepam + phenobarbital)	17.59	1.95	0.53	33.33	20.07
(GDP per capita: US$1135.5 in 2021)		Long-term management (phenobarbital)	8.96	1.94	0.53	20	11.42
	Migraine	First-line analgesics (ASA)	5.03	0.22	0.53	20	5.79
		First-line analgesics (ASA) + prophylaxis	5.03	3.24	0.53	33.33	8.80
	Dementia	Cholinesterase inhibitors	10.34	620.50	0.53	50	631.38
		SSRIs	10.34	3,50	0.53	33.33	14.38
		Caregivers of dementia patients	0.90	n/a	0.53	20	1.43
	Parkinson's disease	Drug treatment: Mild	5.87	69.75	0.53	50	76.50
		Moderate	5.87	109.61	0.53	50	116.01
		Severe	5.87	159.43	0.53	50	168.45
		Basic physical therapy	17.39	n/a	0.53	25	17.92

US$: 2021 US dollars

Sensitivity intervals were calculated by increasing and decreasing costs and effects by an uncertainty factor (see *Data analysis*)

Country-specific HR-costs were estimated using salary databases and verified by the local experts. HR-costs include annual salary, number of workdays a year, and number of hours that health care staff works per day. HR-costs per patient was calculated based on the amount of time each health worker spends on in- and out-patient care per patient in different health platforms (hospital, health centers, or community). As diagnosis is a prerequisite for treatment, these costs (based on a 30-minute assessment with a neurologist and 10 minutes for vital sign testing with a nurse) were calculated and spread equally across the scaleup period of 10 years.

Drug costs were calculated and verified by the local experts with respect to costing, daily and annual dosage, and availability. Drug costs for each condition were extracted from the Management Sciences for Health Drug Price Indicator Guide [83].

Data analysis

Based on the cost and effectiveness, CEAs for the selected interventions were carried out using FairChoices – DCP Analytics Tool (FairChoices), a web-based tool for health economic evaluations of health interventions [47]. Because the interventions were mutually exclusive, they can be ranked according to the incremental cost-effectiveness ratio (ICER).

Healthy life expectancy (HLE) was calculated for each intervention using sex- and age-specific disability weights with and without the intervention giving the following formula for sex- and age-specific HLYs gained:

HLYs gained = HLE(with intervention) – HLE(without intervention).

Other outcome measures were costs, and ICERs (US$ per HLY). The three outcome measures were calculated over a 10-year time horizon. The outcome was calculated for a 10 percentage points (pp) increase from baseline coverage. The scale-up was linear across the 10-year period. All analyses were initially conducted with a 3% discount rate for costs and

effectiveness. We also conducted a set of analyses using no discount rate, as well as a more ambitious scale-ups of 25pp and 40% pp increase from baseline coverage.

A one-way sensitivity analysis was conducted to account for uncertainty in the input parameters, providing a lower and upper bound for both the costs and efficacy numbers of what we assume are realistic parameters. To determine an upper and lower bound for costs, the estimated level of uncertainty of the calculated costs was factored in by multiplying or dividing the unit costs, ranging between 20% for drugs prices listed in the MSH Drug Price Indicator Guide to 50% of the costs not taken up into this price guide (see Table 2 and Table 3). For outdated cost information, 30-40% was used. A similar approach was conducted for the effectiveness, depending on the level of certainty of the evidence, ranging from 25% for meta-analyses and systematic reviews, to 50% of the effectiveness for stand-alone studies. In the best-case scenario, the lower bound for costs was combined with the upper bounds for increased effectiveness, whereas in the worst-case scenario, the bounds for higher costs combined with lower effectiveness was used. We expect the cost-effectiveness to be within this range.

Ethical considerations

Approval from Norwegian and local ethics committees is not necessary, because this project is based on publicly available data at an aggregate level. No data on individuals will be used.

Results

For all the neurological interventions in each different setting, the HLYs and budget impact was determined for scale-up of 10 percentage points (pp) with 3% discounting (Table 4; Table 5) over a period of 10 years. Scale-up for the target coverages of 25pp and 40pp scale-up, as well as the results of the one-way sensitivity analysis for these target coverages can be found in Supplementary Tables S1 and S2. The ICERs did not change much in the undiscounted analyses

(see Supplementary file Tables S3 and S4, and Figure S1). The ICERs for 10% scale-up are listed in Figure 1, as scale-up is assumed linear in time with a constant unit cost. For brevity, in this results section M denotes millions and K denotes thousands.

Table 4: the total health gains and budget impact (US$) for all interventions with 10 percentage points scale-up with 3% discounting

		10pp coverage increase					
		Ethiopia		Malawi		Tanzania	
Condition	Treatment	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)
Epilepsy	Acute stablization	17 214	2 999	3 540	436	14 754	1 606
	Long-term management	119 642	1 891	25 361	276	90 321	753
Migraine	ASA	80 295	18 778	15 368	2 351	48 482	7 097
	ASA + prophylaxis	129 708	43 872	24 825	5 318	78 317	10 652
Dementia	Cholinesterase inhibitors	3 647	127 102	629	13 796	2 145	22 964
	SSRIs	912	1 472	157	169	536	523
	Caregivers of dementia patients	1 999	165	343	10	1 182	111
Parkinson's disease	Total drugs for Parkinson's disease	181	2 466	32	275	324	1 419
	Mild phase	13	575	2	64	21	300
	Moderate phase	120	862	22	96	205	457
	Severe phase	47	1 029	8	115	98	663
	Basic physical therapy	627	117	111	15	377	71

Health Gains for 10% scale-up

As seen in Table 4, the three interventions with the highest health gains in all three settings were long-term management of epilepsy (Ethiopia: 120K; [best-case: 139K- worst case: 104K]; Malawi: 25K [30K-22K]; Tanzania 90K [104K-80K]), ASA against migraine (Ethiopia: 80K; [100K- 64K]; Malawi: 15K [19K-12K]; Tanzania 49K[61K-39K]), and ASA with prophylaxis against migraine (Ethiopia: 130K; [173K - 98K]; Malawi: 25K [33K-19K]; Tanzania 78K[104-59K]). Scaling up treatment of epilepsy and migraine would yield the most HLYs gained. For migraine, the HLYs gained increased by 150% when prophylaxis was included in the management of migraine for the subpopulation that benefits from this

intervention. Out of the three dementia interventions, drug treatment with cholinesterase inhibitors had the highest number of HLYs gained, around four times as high as drug treatment with SSRIs across all three settings. As drug effectiveness declines throughout the three phases of Parkinson's disease, as do the HLYs gained. The health gains of drug treatment in the mild phase of Parkinson's disease are 2.5 to 12 times as high compared to the moderate phase and severe phase of the disease.

Budget impact for 10% scale-up

Table 4 shows that in all three countries the interventions with the smallest budget impact are basic physical therapy for Parkinson's disease (Ethiopia: 117K [93K; 146K]; Malawi: 15K [12;19]; Tanzania: 71K [56;88]), and caregivers of dementia patients (Ethiopia: 165K [138K; 198K]; Malawi: 10K [8K;12K]; Tanzania: 111K [92K;133K]). Scaling up cholinesterase inhibitors has the highest budget impact (Ethiopia: 127.1M [84.7M; 190.7M]; Malawi: 13.8M [9.2M; 20.7M]; Tanzania: 23.0M [15.3M; 34.4M]). For migraine, treatment with first-line pain killers and prophylaxis are 1.5 times more expensive than treatment with first-line pain killers alone across the three settings. As Parkinson's medication wears off over time, patients need to take more medication as the disease progresses, which explains why costs increase for the different treatment phases in all three settings (Ethiopia: 2.5M [1.6M; 3.7M]; Malawi: 275K [183K-413K]; Tanzania:1.4M [946K; 2.1M].

Figure 1: US$/HLY (ICERs) for 10 pp coverage increase over 10 years with 3% discounting

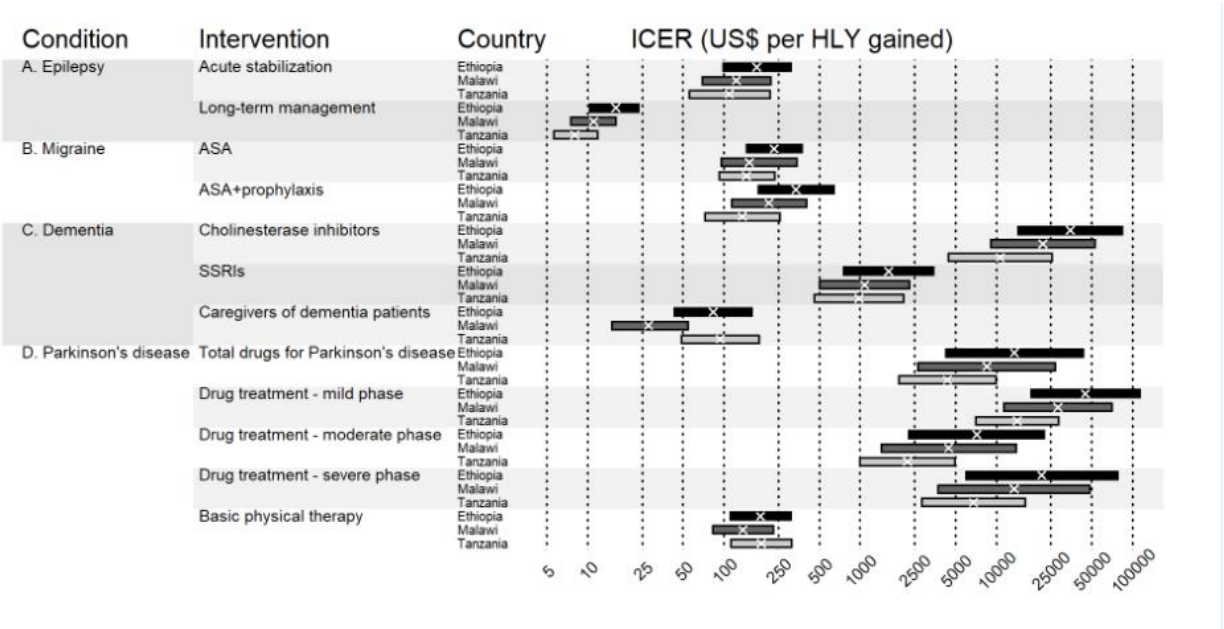

Table 5: Sensitivity analysis for 10 pp coverage over 10 years with 3% discounting

			10pp coverage increase								
			Ethiopia			Malawi			Tanzania		
Condition	**Treatment**	**Scenario**	**ICER**	**Health gains**	**Budget impact US$ (thousands)**	**ICER**	**Health gains**	**Budget impact US$ (thousands)**	**ICER**	**Health gains**	**Budget impact US$ (thousands)**
Epilepsy	Acute stablization	Best-case	105	21 518	2 255	74	4 425	328	58	20 656	1 208
		Worst-case	290	13 772	3 989	205	2 832	580	203	10 539	2 136
	Long-term management	Best-case	11	138 794	1 576	8	29 489	230	6	103 680	628
		Worst-case	22	104 321	2 269	15	22 059	331	11	79 634	904
	ASA	Best-case	156	100 369	15 648	102	19 210	1 959	98	60 603	5 914
		Worst-case	351	64 236	22 533	229	12 294	2 821	220	38 786	8 517
	ASA + prophylaxis	Best-case	191	172 511	32 987	121	33 018	3 999	77	104 162	8 009
		Worst-case	598	97 525	58 350	379	18 666	7 073	241	58 885	14 167
	Cholinesterase inhibitors	Best-case	15 490	5 470	84 734	9 756	943	9 197	4 757	3 218	15 309
		Worst-case	78 416	2 431	190 652	49 388	419	20 694	24 083	1 430	34 445
	SSRIs	Best-case	809	1 368	1 107	539	236	127	489	805	393
		Worst-case	3 221	608	1 958	2 146	105	225	1 946	358	696
	Caregivers of dementia patients	Best-case	46	2 999	138	16	515	8	52	1 773	92
		Worst-case	149	1 333	198	51	229	12	169	788	133
	Total drugs for Parkinson's disease	Best-case	4 533	363	1 644	2 831	65	183	2 056	460	946
		Worst-case	40 799	91	3 699	25 480	16	413	9 314	229	2 129
	Mild phase	Best-case	19 287	20	383	12 069	4	43	7 582	26	200

	Worst-case	105 945	8	863	66 297	1	96	26 654	17	450
Moderate phase	Best-case	2 436	236	575	1 522	42	64	1 059	287	304
	Worst-case	13 961	61	1 294	13 152	11	144	4 672	147	685
Severe phase	Best-case	6 421	107	686	4 006	19	76	3 017	147	442
	Worst-case	73 135	21	1 543	45 625	4	172	15 275	65	995
Basic physical therapy	Best-case	119	784	93	88	138	12	120	471	56
	Worst-case	290	502	146	216	89	19	292	302	88

pp (percentage points)

US$: 2021 US dollars

Cost-effectiveness

In all three settings, the same six interventions were considered the most cost-effective interventions (Figure 1). Both acute stabilization of epilepsy (ICER in Ethiopia 174 [best-case: 105; worst-case: 290]; ICER in Malawi 123 [74; 205]; ICER in Tanzania 109 [59; 203]), and long term management of epilepsy (Ethiopia: 16 [11; 22]; Malawi: 11 [8;15]; Tanzania: 8 [6; 11]) were included, as well as ASA against migraine (Ethiopia: 234 [156; 351]; Malawi: 153 [102; 320]; Tanzania: 146 [98; 220]) and ASA + prophylaxis (Ethiopia: 338 [191; 598]; Malawi: 214 [121; 379],Tanzania: 136 [77; 241]), caregivers of dementia patients (Ethiopia: 83 [46; 149]; Malawi: 28 [16; 51]; Tanzania: 94 [52; 169]), and basic physical therapy for Parkinson's disease (Ethiopia: 186 [119; 290]; Malawi: 138 [88; 216]; Tanzania: 187 [120; 292]). For these interventions, even the worst-case scenario ICERs were 598 US$ per HLY gained or less in all countries. The gold standard for dementia drug treatment, cholinesterase inhibitors, had the highest ICERs in all countries (Ethiopia: 34 852 [15 490;78 416]; Malawi: 21 950 [9756;49 388]; Tanzania: 10 704 [4 757; 24 083]).

ICERs were generally lower in Tanzania than in Malawi, and lower in Malawi than in Ethiopia (Figure 1). Exceptions to this pattern was caregivers of dementia patients, and basic physical therapy for Parkinson's patients.

Discussion

This cost-effectiveness analysis provides evidence of the health gains and budget impact to be gained by scaling up the 10, 25 and 40 pp coverage of neurological interventions. Acute stabilization and long-term management for epilepsy, caregivers for dementia patients, basic physical therapy for Parkinson's disease and first-line analgesics (with and without prophylaxis) in migraine management are the most cost-effective interventions in all the countries. The interventions with the highest costs per HLY gained were drug treatment for Parkinson's disease and the gold standard for dementia treatment, cholinesterase inhibitors. These interventions have high ICERs due to a lack of baseline coverage, accurate costs, as well as the neurodegenerative nature of the disease that cannot be halted. This results in high ICERs and a wide interval in the sensitivity analysis. In Parkinson's disease, the added downside is that more medication needs to be taken in the later phases for it to still be effective, driving up the costs even more. The two epilepsy interventions had low ICERs in the three settings.

For epilepsy, one study on the East Africa region reports an ICER of US$265 per HLY gained for treatment with phenobarbital [62]. This study included program costs, along which costs for system administration, policy development, and training. Similar evidence for the same region yields an ACER of US$76 for treatment with phenobarbital [63] and was costed according to the WHO-Choice costing paper [84]. Lastly, a cost-effectiveness analysis in Ethiopia yielded an ICER of 321 US$ per DALY averted [64]. In this study, a micro-costing approach was used that also includes facility costs. The current calculated ICERs of 174 US$/HLY(Ethiopia), 123 US$/HLY (Malawi), and 109 US$/HLY (Tanzania) is based on direct health costs only, as no health system or facility costs were taken into consideration. However, our input parameters on cost for treatment and effect are similar to what these articles show, suggesting that the differences found can largely be explained by the additional

health system and miscellaneous costs. Furthermore, these studies do not provide evidence on acute stabilization for epileptic seizures.

For migraine, a previous study carried out in Zambia reported an ICER of $24 for ASA[61], compared to our ICERs of 234 US$/HLY(Ethiopia), 153 US$/HLY (Malawi), and 146 US$/HLY (Tanzania). The authors only assessed drug costs, in comparison to our costs that include costs for diagnosis and follow-up. The cost-effectiveness analysis for first line analgesics combined with prophylaxis yielded an ICER of US$773 per HLY, as compared to our findings of 338 US$/HLY(Ethiopia), 214 US$/HLY (Malawi), and 136 US$/HLY (Tanzania)[61]. These differences in the ICER for prophylaxis can be explained by the differences in drug costs, as in the current study, the costs are based on a three month duration, in comparison to taking one pill per day annually.

For dementia, no cost-effectiveness data is available for drugs treatment in low-income countries. A systematic review, carried out in the United Kingdom, deemed that different cholinesterase inhibitors are cost-effective if the willingness to pay is set to £30 000 per QALY[85], which is not too far off from the outcomes in the current study that yielded ICERs of 34 852 US$/HLY(Ethiopia), 21 950 US$/HLY (Malawi), and 10 704 US$/HLY (Tanzania). As no costing information could be found on cholinesterase inhibitors in low-income countries, evidence from studies on cost and effectiveness in high income countries had to be included. Therefore, the similarity in ICERs is not surprising.

For Parkinson's disease drug treatment, a meta-analysis identified the cost-effectiveness for levodopa/carbidopa/entacapone as £3105 per QALY, in comparison to the current results of ICERs of 13 656 US$/HLY(Ethiopia), 8 529 US$/HLY (Malawi), and 4 381 US$/HLY (Tanzania)[86]. These large differences in ICERs can be explained by the high uncertainty of the drug costs. However, the ICERs of the best-case scenario are comparable to the found outcome of the meta-analysis. For studies on sub-stages of Parkinson’s disease, the evidence

is limited. A review on cost effectiveness of pharmacotherapies in the early phase of Parkinson's disease even concludes that due to different methodologies, it is difficult to conclude on the most cost-effective alternative in this phase[87]. One Australian study identified physical therapy in Parkinson's disease as cost-effective, with $A 574 per fall prevented, $A9570 to combat progression of motor symptoms and $A338 800 per QALY gained in comparison to US$ 186 (Ethiopia), US$ 138 (Malawi) US$ 187 (Tanzania)[88]. These differences are vast, and are caused by methodological differences such as the program costs, and different frequency and duration of the therapy sessions, making these two studies little comparable.

A limitation of this study is that we assume that the unit cost of the interventions is the same regardless of baseline coverage. This may not be true if costs are higher for initial investments when scaling up coverage from very low levels. For example, for drug treatment when no treatment is currently available, health workers may need extra training which they would not need if baseline coverage was already at 25%.

Between all interventions, both the health gains and the budget impact are the lowest in Malawi. The budget impact in Ethiopia is the highest for all interventions, as well as the health gains for all interventions targeting epilepsy, migraine, and dementia, as well as physical therapy in Parkinson's disease. Drug treatment for Parkinson's disease has the most health gains in Tanzania because of the higher prevalence.

The lowest ICERs throughout the most of the interventions are found in Tanzania, despite generally having higher unit costs, as the lowest costs and lowest health gains in Malawi, and the highest costs and highest health gains in Ethiopia balance the ICER out. Only the interventions focused on caregivers of dementia patients and basic physical therapy are lower in Malawi. These differences in findings can be explained by a larger gap in salaries for

clinical health workers in Malawi compared to the other settings, as well as different a prevalence at baseline per country.

The results identify drug treatment in dementia and Parkinson's disease as too little cost-effective, however these interventions do make a vast impact on the quality of life of patients and their family members [89]. These results suggests that the impact shown by the cost-effectiveness analysis alone could benefit from added data on non-health benefits. Therefore, in future research, there is a need to explore a different methodology, that takes these non-health outcomes into consideration in a resource constrained setting.

Either of the selected neurological conditions is broadly underdiagnosed in East-Africa, because of stigmatization, lack of resources or money. Other explanations are remarked as witchcraft, or contrarily seen as part of natural aging. We tried to factor in the underdiagnoses by taking into consideration the most updated numbers on prevalence and incidence, to assume the most realistic parameters available currently remains the best method to approximate a real-life scenario through this modelling exercise. Furthermore, it is assumed that fluctuations that naturally occur within neurological conditions, like disease flare-ups, will be averaged out over time by considering the average case scenario. Additionally, this article only evaluates the effects of a subset of neurological disorders. Other excluded neurological disorders are still contributing tremendously to the high disease burden and high causes of death, but were omitted in part due to limited prevention- or treatment options that are available in LLMICs.

Lastly, for the sole purpose of identifying best-buy interventions, no threshold was chosen, as the willingness to pay is depended on the budget of each country.

This article is a first step in determining the cost-effectiveness of neurological disorders in LLMICs, and future research is needed to obtain new insights on the cost-effectiveness of interventions for the challenges that remain.

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Supplementary file

Table S1: Health gains and budget impact (US$) for target coverages (25pp, 40pp) over 10 years with 3% discounting.

		25pp coverage increase									40pp coverage increase					
		Ethiopia			Malawi			Tanzania			Ethiopia		Malawi		Tanzania	
Condition	Treatment	ICER	Health gains	Budget impact US$ (thousands)	ICER	Health gains	Budget impact US$ (thousands)	ICER	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)
Epilepsy	Acute stablization	174	43 036	7 498	123	8 849	1 066	109	36 885	4 016	68 859	11 997	14 159	1 706	59 017	6 425
	Long-term management	16	299 106	4 728	11	63 404	666	8	225 803	1 883	478 572	7 564	101 446	1 065	361 287	3 014
Migraine	ASA	234	200 738	46 944	153	38 420	5 404	146	121 205	17 743	321 181	75 111	61 472	8 646	193 928	28 389
	ASA + prophylaxis	338	324 269	109 681	214	62 063	128 226	136	195 793	26 630	518 831	175 489	99 302	20 516	313 269	42 607
Dementia	Cholinesterase inhibitors	34 852	9 117	317 754	21 950	1 571	34 480	10 704	5 364	57 409	14 588	508 406	2 514	55 168	8 582	91 854
	SSRIs	1 615	2 279	3 680	1 076	393	412	975	1 341	1 308	3 647	5 888	629	659	2 145	2 093
	Caregivers of dementia patients	83	4 998	413	28	858	24	94	2 954	277	7 997	661	1 372	39	4 727	443
Parkinson's disease	Total drugs for Parkinson's drugs	13 656	451	6 166	8 529	81	687	4 381	810	3 549	722	9 865	129	1 099	1 296	5 678
	Mild phase	45 203	32	1 438	28 287	6	160	14 215	53	749	51	2 300	9	257	84	1 199
	Moderate phase	7 163	301	2 156	4 473	54	240	2 224	513	1 142	482	3 450	86	384	821	1 827
	Severe phase	21 670	119	2 572	13 519	21	286	6 789	244	1 658	190	4 115	34	458	391	2 652
	Basic physical therapy	186	1 569	291	138	277	37	187	943	176	2 510	466	443	59	1 509	282

Table S2: Best- and worst-case scenario (one-way sensitivity analysis) for 25- and 40 pp increase in target coverage with 3% discounting.

			25pp coverage increase						40pp coverage increase					
			Ethiopia		Malawi		Tanzania		Ethiopia		Malawi		Tanzania	
Condition	Treatment	Scenario	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)	Health gains	Budget impact US$ (thousands)
Epilepsy	Acute stablization	Best-case	53 795	5 638	11 062	820	51 640	3 019	86 073	9 021	17 699	1311	82 624	4 831
		Worst-case	34 429	9 973	7 079	1 450	26 347	5 341	55 087	15 956	11 327	2 320	42 155	8 546
	Long-term management	Best-case	346 985	3 940	73 724	575	259 201	1 570	555 178	6 303	117 959	919	414 723	2 511
		Worst-case	260 803	5 673	55 148	828	199 085	2 260	417 287	9 077	88 237	1 324	318 538	3 616
Migraine	ASA	Best-case	250 923	39 120	48 025	4 898	151 507	14 786	401 476	62 592	76 841	7 837	242 411	23 658
		Worst-case	160 590	56 333	30 736	7 053	96 964	21 292	256 945	90 133	49 178	11 285	155 143	34 067
	ASA + prophylaxis	Best-case	431 278	82 467	82 544	9 997	260 405	20 022	690 045	131 947	132 071	15 995	416 648	32 036
		Worst-case	243 811	145 876	46 664	17 684	147 213	35 417	390 098	233 401	74 663	28 294	235 541	56 668
Dementia	Cholinesterase inhibitors	Best-case	13 676	211 836	2 357	22 994	8 045	38 273	21 882	338 937	3 771	36 790	12 873	61 236
		Worst-case	6 078	476 631	1 048	51 736	3 576	86 113	97 25	762 609	1 676	82 777	5 721	137 781
	SSRIs	Best-case	3 419	2 767	589	318	2 011	983	5 470	4 427	943	508	3 218	1 573
		Worst-case	1 520	4 895	262	562	894	1 739	2 431	7 831	419	8 99	1 430	2 783
	Caregivers of dementia patients	Best-case	7 497	344	1 286	20	4 431	231	11 995	551	2 058	32	7 090	369
		Worst-case	3 332	496	572	29	1 970	332	5331	793	915	47	3 151	532
Parkinson's disease	Total drugs for Parkinson’s disease	Best-case	907	4 110	162	459	1 151	2 366	1 451	6 577	259	734	1 841	3 785
		Worst-case	227	9 248	41	1 032	572	5 323	363	14 797	65	1 651	914	8 517
	Mild phase	Best-case	50	958	9	107	66	500	80	1 534	14	171	105	799
		Worst-case	20	2 157	4	241	42	1 124	33	3 451	6	386	76	1 799
	Moderate phase	Best-case	590	1 437	105	160	718	761	944	2 300	169	257	1 149	1 218
		Worst-case	154	3 234	27	361	367	1 712	246	5 175	44	577	586	2 740
	Severe phase	Best-case	267	1 714	48	191	366	1 105	3427	2 743	76	306	586	1 768
		Worst-case	53	3 858	9	430	163	2 487	84	6 172	15	688	260	3 978

Basic physical therapy	Best-case	1 961	233	346	31	1 179	141	3137	373	554	49	1 886	226
	Worst-case	1 255	364	222	48	754	220	2008	583	354	76	1207	353

pp (percentage points)

US$: 2021 US dollars

Table S3: US$/HLY, costs, HLY for target coverages (10pp, 25pp, 40pp) over 10 years without discounting

Country / intervention	Treatment	ICER	10pp coverage increase		25pp coverage increase		40pp coverage increase	
		$/HLY	HLYs gained	Costs US$ (thousands)	HLYs gained	Costs US$ (thousands)	HLYs gained	Costs US$ (thousands)
Ethiopia								
Epilepsy	Acute stablization	106	33 625	3 572	84 062	8 930	134 500	14 287
	Long-term management	14	162 190	2 252	405 476	5 630	648 763	9008
Migraine	ASA	273	81 887	22 362	204 719	55 905	327 550	89 448
	ASA + prophylaxis	395	132 280	52 247	330 699	130 617	529 119	208 988
Dementia	Cholinesterase inhibitors	40 684	3 720	151 363	9 301	378 408	14 882	605 453
	SSRIs	1 885	930	1 753	2 325	4 383	3 720	7 012
	Caregivers of dementia patients	97	2 040	197	5 099	492	8 159	787
Parkinson's disease	Total drugs for Parkinson's disease	15 945	184	2 937	460	7 342	737	11 748
	Mild phase	52 782	13	685	32	1 712	52	2 740
	Moderate phase	8 364	123	1 027	307	2 568	491	4 108
	Severe phase	25 303	48	1 225	121	3 063	194	4 900
	Basic physical therapy	217	640	49	1600	124	2560	198
Malawi								
Epilepsy	Acute stablization	77	6 712	519	16 781	1 298	26 850	2 077
	Long-term management	10	33 621	328	84 053	821	134 485	1 314
Migraine	ASA	179	15 673	2 800	39 182	7 000	62 690	11 199
	ASA + prophylaxis	250	25 37	6 334	63 293	15 834	101 269	25 344
Dementia	Cholinesterase inhibitors	25 624	641	16 430	1 603	41 074	2 565	65 719
	SSRIs	1 256	160	201	401	503	641	805
	Caregivers of dementia patients	33	350	12	875	29	1 400	46
Parkinson's disease	Total drugs for Parkinson's disease	9958	33	328	82	819	132	1 311
	Mild phase	33 029	2	77	6	191	9	306

	Moderate phase	5 223	22	115	55	287	88	458
	Severe phase	15 785	9	137	22	341	35	546
	Basic physical therapy	161	113	18	282	46	452	73
Tanzania								
Epilepsy	Acute stablization	66	29 171	1 913	72 929	4 782	116 687	7 652
	Long-term management	7	127 424	897	318 562	2 243	509 702	3 589
	ASA	171	49 442	8 452	123 606	21 130	197 770	33 808
Migraine	ASA + prophylaxis	159	79 869	12 685	199 671	31 713	319 474	50 740
Dementia	Cholinesterase inhibitors	12 495	2 189	27 347	5 471	68 367	8 754	109 388
	SSRIs	1 139	547	623	1 368	1 557	2 189	2 492
	Caregivers of dementia patients	109	1 206	132	3 014	330	4 822	528
Parkinson's disease	Total drugs for Parkinson's disease	5 115	330	1 690	826	4 226	1322	6 762
	Mild phase	16 599	22	357	54	892	86	1 428
	Moderate phase	2 598	209	544	523	1 360	837	2 175
	Severe phase	7 927	100	790	249	1 974	398	3 159
	Basic physical therapy	218	385	84	962	210	1 539	336

Figure S1: HLY/US$ 10 pp coverage increase over 10 years without discounting

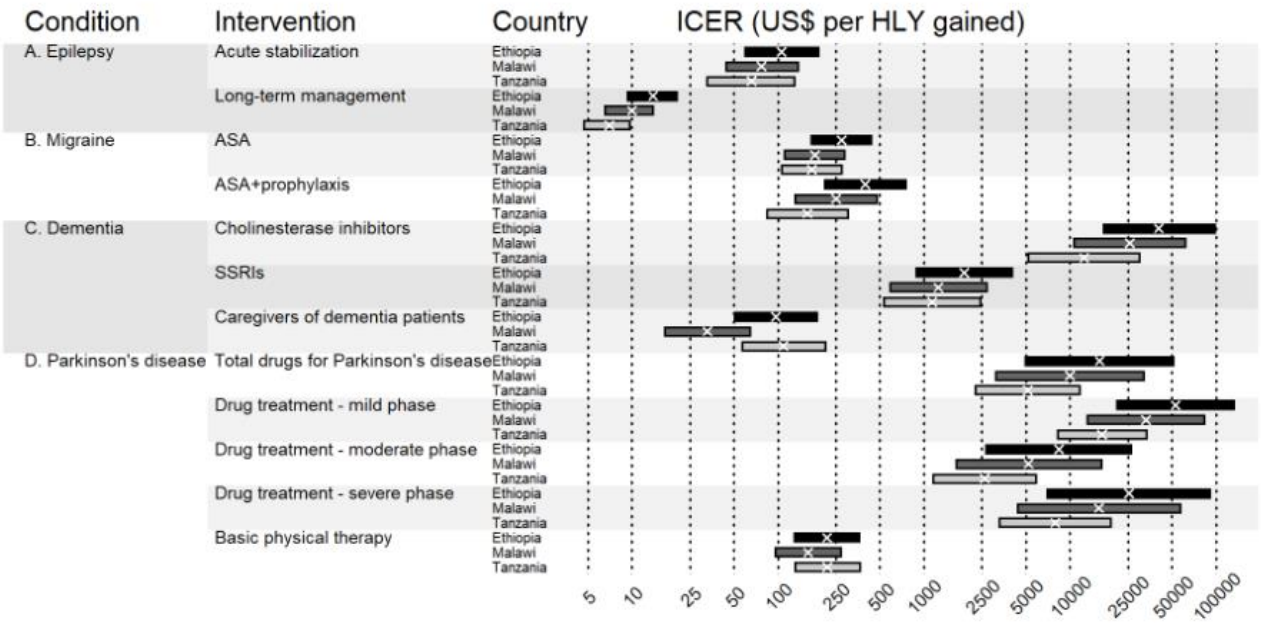

Table S4: Best- and worst-case scenario (one way sensitivity analysis) for 10-, 25- and 40 pp (percentage points) increase in target coverage without discounting.

				10pp coverage increase		25pp coverage increase		40pp coverage increase	
Country	Treatment	Scenario	ICER	HLY	Costs (US$)	HLY	Costs (US$)	HLY	Costs (US$)
Ethiopia									
Epilepsy	Acute stablization	Best-case	64	42 031	2 686	105 077	6 714	168 124	10 742
		Worst-case	177	26 900	4 751	67 249	11 876	107 600	19 002
	Long-term management	Best-case	10	181 722	1 877	454 306	4 692	726 892	7 507
		Worst-case	18	146 564	2 702	366 411	6 756	586 260	10 809
Migraine	ASA	Best-case	182	102 359	18 635	255 898	46 588	409 437	74 540
		Worst-case	410	65 510	26 835	163 775	67 086	262 040	107 338
	ASA + prophylaxis	Best-case	223	175 932	39 283	439 830	98 208	703 728	157 133
		Worst-case	699	99 458	69 488	248 646	173 721	397 834	277 953
Dementia	Cholinesterase inhibitors	Best-case	18 082	5 581	100 909	13 952	252 272	22 323	403 635
		Worst-case	91 539	2 480	227 045	6 201	567 612	9 921	908 179
	SSRIs	Best-case	945	1 395	1 318	3 488	3 295	5 581	5 272
		Worst-case	3 760	620	2 332	1 550	5 829	2 480	9 326
	Caregivers of dementia patients	Best-case	54	3 059	164	7 649	410	12 238	656
		Worst-case	174	1 360	236	3 399	591	5 439	945
Parkinson's disease	Total drugs for Parkinson's disease	Best-case	5 293	370	1 958	925	4 895	1480	7 832
		Worst-case	47 639	92	4 405	231	11 014	370	17 622
	Mild phase	Best-case	22 520	20	457	51	1 141	81	1 826
		Worst-case	123 707	8	1 027	21	2 568	33	4 109
	Moderate phase	Best-case	2 845	241	685	602	1 712	963	2 739
		Worst-case	24 589	63	1 541	157	3 851	251	6 162
	Severe phase	Best-case	7 497	109	817	272	2 042	436	3 267
		Worst-case	85 396	22	1 838	54	4 594	86	7 350
	Basic physical therapy	Best-case	139	800	111	2 000	278	3 200	444
		Worst-case	339	512	173	1 280	434	2 048	694

Table S4, continued: Best- and worst-case scenario (one way sensitivity analysis) for 10-, 25- and 40 pp (percentage points) increase in target coverage without discounting.

				10pp coverage increase		25pp coverage increase		40pp coverage increase	
Country	Treatment	Scenario	ICER	HLY	Costs (US$)	HLY	Costs (US$)	HLY	Costs (US$)
Malawi									
Epilepsy	Acute stablization	Best-case	47	8 391	390	20 977	976	33 563	1 562
		Worst-case	129	5 370	691	13 425	1 727	21 480	2 763
	Long-term management	Best-case	7	37 831	274	94 578	684	151 325	1 095
		Worst-case	13	30 253	394	75 633	985	121 013	1 577
Migraine	ASA	Best-case	119	19 591	2 333	48 977	5 833	78 363	9 333
		Worst-case	248	12 538	3 360	31 345	8 400	50 152	13 439
	ASA + prophylaxis	Best-case	141	33 672	4 762	84 180	11 905	134 688	19 048
		Worst-case	443	19 036	8 424	47 589	21 059	76 142	33 695
Dementia	Cholinesterase inhibitors	Best-case	11 389	962	10 953	2 404	27 383	3 847	43 803
		Worst-case	57 655	427	24 645	1 069	61 611	1 710	98 578
	SSRIs	Best-case	629	240	151	601	378	962	605
		Worst-case	2 505	107	268	267	669	427	1 071
	Caregivers of dementia patients	Best-case	18	525	10	1 312	24	2 100	39
		Worst-case	60	233	14	583	35	933	56
Parkinson's disease	Total drugs for Parkinson's disease	Best-case	3 306	66	219	165	546	264	874
		Worst-case	29 752	17	492	41	1 229	66	1 967
	Mild phase	Best-case	14 092	4	51	9	128	14	204
		Worst-case	77 411	1	115	4	287	6	459
	Moderate phase	Best-case	1 777	43	76	108	191	172	305
		Worst-case	15 356	11	172	28	430	45	688
	Severe phase	Best-case	4 677	19	91	49	228	78	364
		Worst-case	53 273	4	205	10	512	15	819
	Basic physical therapy	Best-case	103	141	15	353	36	565	58
		Worst-case	252	90	23	226	57	362	91

Table S4, continued: Best- and worst-case scenario (one way sensitivity analysis) for 10-, 25- and 40 pp (percentage points) increase in target coverage without discounting.

				10pp coverage increase		25pp coverage increase		40pp coverage increase	
Country	Treatment	Scenario	ICER	HLY	Costs (US$)	HLY	Costs (US$)	HLY	Costs (US$)
Tanzania									
Epilepsy	Acute stablization	Best-case	35	40 840	1 438	102 100	3 596	163 361	5 753
		Worst-case	122	20 837	2 544	52 092	6 361	83 348	10 177
	Long-term management	Best-case	5	141 048	748	352 622	1 869	564 199	2 991
		Worst-case	9	116 525	1 077	291 314	2 692	466 105	4 307
Migraine	ASA	Best-case	114	61 803	7 043	154 508	17 609	247 212	28 174
		Worst-case	256	39 554	10 143	98 885	25 356	158 216	40 570
	ASA + prophylaxis	Best-case	90	106 225	9 538	265 563	23 844	424 901	38 151
		Worst-case	281	60 052	16 871	150 129	42 178	240 206	67 485
Dementia	Cholinesterase inhibitors	Best-case	5 553	3 283	18 231	8 207	45 578	13 131	72 925
		Worst-case	28 114	1 459	41 020	3 648	102 551	5 836	164 082
	SSRIs	Best-case	571	821	468	2 052	1 171	3 283	1 874
		Worst-case	2 272	365	829	912	2 071	1 459	3 314
	Caregivers of dementia patients	Best-case	61	1 808	110	4 521	275	7 234	440
		Worst-case	197	804	158	2 009	396	3 215	633
Parkinson's disease	Total drugs for Parkinson's disease	Best-case	2 401	469	1 127	1 173	2 817	1 878	4 508
		Worst-case	10 876	233	2 536	583	6 339	933	10 143
	Mild phase	Best-case	8 853	27	238	67	595	108	952
		Worst-case	31 123	17	535	43	1 339	69	2 142
	Moderate phase	Best-case	1 237	293	363	733	906	1 172	1 450
		Worst-case	5 455	150	816	374	2 039	598	3 263
	Severe phase	Best-case	3 523	149	526	374	1 316	598	2 106
		Worst-case	17 835	66	1 184	166	2 961	266	4 738
	Basic physical therapy	Best-case	140	481	67	1 202	168	1 924	269
		Worst-case	341	308	105	769	263	1 231	420

pp (percentage points)
HLYs (healthy life years)
US$: 2021 US dollars
*See Box 1 for explanations of labels

Appendix 2: Background of the neurological disorders, interventions, and model input parameters

Appendix 2.1 Epilepsy: diagnostics and treatment

Authors: J. Hubbers, Ahmed S, Watkins D, Coates MM, Økland JM, Haaland ØA, Johansson KA

Date: December 12th, 2021

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*deopathic epilepsy*, 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%[64, 72-76]. 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

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

Description of disorder 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 [24]. Epilepsy can be genetic or acquired. The manifestation usually peaks before the 20th 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 [24].

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 [24]. 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 [24].

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 [90]. Limited literature can be found for the prevalence of the other subtypes of epilepsy in Africa. Table 3 shows some key epidemiologic parameters for epilepsy.

Table 3: 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
Idiopathic epilepsy				
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 [90]. 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 [25].

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 [25]. 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% [64]. 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 [91], and WHO found similar results in 9 low-income regions worldwide [92].

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 [93].

Table 4. 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 [94]	√

Type of intervention

Chronic management care

Delivery platform

Health centre is suggested to be the primary delivery, although severe and complicated cases should 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 disorder 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 disorder. FairChoices shows for each intervention an average HAAD value of the disorders that are affected by respective interventions that have health effects. Additionally, a plot shows HAAD values for around 290 conditions[95].

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 [24]. 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 [90].As a comparison, the prevalence of epilepsy in West-Africa is 13.14 per 1000 [96]. In FairChoices, we have country specific prevalence data from GBD [1, 97].

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 [98, 99], 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 [64]). 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 [100]). 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[101]).

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 5: 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 6: 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 7: 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

Table8: Drug/supply component for treatment of epilepsy

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 9: Total unit costs

	Total HR Costs LIC(in US$)	Total HR Costs LMIC (in US$)	Total drug costs [83]	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

References

References included in the main reference list.

Appendix 2.2 Self-managed treatment of migraine

Author: J Hubbers, Ahmed S, Watkins D, Coates MM, Økland JM, Haaland ØA, Johansson KA

Date: December 12th, 2021

Model assumptions

Table 1: Summary of model parameters and values used for self-management of migraine in FairChoices – DCP Analytics Tool

Population:	All prevalent cases of migraine, both genders, all ages (Dw=0.44 in average untreated)
Intervention	Self-managed treatment of migraine with stepwise approach (stop at lowest effective level) – Step 1: Nonpharmacological interventions (30% assumed to need this) – Step 2: First line drugs (Paracetamol, NSAIDS, ASA) when acute attacks (50% need this) *– Step 3: Triptans when acute attacks (currently not included in analysis)* – Step 4: Prophylaxis (38% of patients assumed to need this)
Comparator	No intervention
Outcome	Disability weight (health related quality of life)
Effect	Total effect of stepwise approach: 63% reduction of disability or improvement of HRQoL
Unit cost*	Diagnostics and education about nonpharmacological interventions: 2.1 US$ LIC; 5.9 US$ LMIC Drugs for migraine – First line drugs: 2.1 US$ LIC; 5.3 US$ LMIC – Prophylaxis: 4.8 US$ LIC; 8.1 US$ LMIC

HRQoL= Health Related Quality of Life

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

Description of condition and intervention

Migraine is often described as a primary headache disorder. Usually, the headache starts off as a dull pain, and then progresses into a throbbing headache, typically presented as a unilateral, meaning one-sided pain (a two-sided, bilateral pain occurs in a third of the cases). Migraine comes in periodic attacks, and its headaches are most often accompanied by an overall feeling of malaise, nausea, and light- and sound sensitivity. Attacks can last between a few hours up to 3 days, but most migraine attacks are resolved in under 24 hours [102].

In general, migraine comes in three subtypes:

- Migraine with aura (classical migraine)
- Migraine without aura (common migraine)
- Migraine aura without headache

Aura is defined as a warning sign, as it often precedes the migraine, and occurs in about 10-20% of migraine cases. Aura most often presents visually, like flickering lights, dark spots or the sensation of “seeing stars”, or zig-zag lines. Other symptoms that are related to auras and migraines are tingling of the hands or face, changes in touch, taste or scent, or feeling, but in severe migraine, the symptoms can result in temporary loss of

strength on one side of the body, also known as hemiplegia or full aphasia, where patients lose the ability to speak temporarily [103].

Migraine attacks can be disabling, as any type of activity usually worsens the attack. During an attack, most patients prefer to lay down in a quiet, dark room to try and rest, as sleep can put a halt to the attacks [103]. It is estimated that over 10% of the world's population suffers from migraines [102]. The prevalence of migraine in Africa is estimated to be greater than 5% [103]. Globally, around 1 128 000 000 people suffer from migraines and global incidence is 3 87 650 000, and migraine accounts for 42 078 000 DALYs.

The onset of migraine generally occurs in two peaks, either during early adolescence or before the age of 40 years old [103], but mostly affects the people between the ages of 35-45 [102], mostly women (2:1).

Diagnosis of migraine:

Migraine is diagnosed by carrying out diagnostic interviews by assessing the length, location, pain intensity and level of aggravation of the attack(s), as well as asking about light sensitivity, and other physiological responses (such as nausea). To determine if a patient is also presenting with aura, the physician asks if there are any changes in vision, sensations, speech, or movement [104]. Other differential diagnoses, like stroke, have to be ruled out.

Socio-economic burden of migraine:

The GBD estimated that migraine is one of the main conditions that lead to a high morbidity globally [68]. The years lived with disease and therefore DALYs are expected to increase due to the growing population, and as a result of the high migraine prevalence in a productive group of people, costs are expected to increase [105]. Migraine attacks hinder people from working or studying, and hence causes high socio-economic consequences. It was estimated that about 2/3rd of the costs of migraine are because of indirect costs, which can be explained by reduced productivity, or absenteeism in work or school [106]. Because of the lack of knowledge and awareness about the migraine, the socioeconomic burden is underestimated, and the disease remains underdiagnosed and undertreated, which can result into governments not realizing the economic benefits of treatment and prevention [102].

Treatment of migraine:

Migraine can be caused by high amounts of stress. Research on the role of coping strategies for stress reduction as self-management of migraine is not conclusive, as most research is focused on pharmacological treatment in high-income countries. Multiple nonpharmacologic treatments for migraine exists: Educating patients about headache and its management, identifying and managing triggers (via diaries) and modifying lifestyles. Mérelle and colleagues [107] assessed the effectiveness of group training through relaxation exercises on the frequency of migraine attacks and found a significant reduction of migraine attacks after a six-month follow-up. It could be beneficial to introduce these kind of group trainings in LLMICs to explore the effect of these low-cost coping strategies further in such settings[25].

Nonpharmacological treatments are combined with various medications, and are typically treated in a step-wise approach, and treatment stops at the lowest cost step that is effective. Drug treatment focusses on treating the acute headache initially with common painkillers like paracetamol, as well as anti-inflammatory painkillers, also known as NSAIDS, and include Ibuprofen, Diclofenac and Naxproxen. Second-line drugs are often magnesium or triptans, a category of medications that can be utilized when painkillers or the anti-inflammatory painkillers are not effective during the acute attack. The efficacy of magnesium treatment is debated. A third drug treatment option is that of prophylaxis with propranolol or amyltriptyline (or estrogen contraceptives for females), which focusses on prevention of the migraine attacks [25, 103].

Table 2: International guidelines for migraine treatment

Organization	Guidelines for treatment and management of migraine	Applicability in LIC & Lower MIC settings

World Health Organization & *Lifting The Burden* (2011)	Atlas of Headache Disorders and Resources in the World, 2011[108]	√
International Headache Society	International Classification of Headache Disorders (ICHD) (3rd Edition), 2018 [104]	√

Type of interventions

Chronic management care

Delivery platform

Health center and community

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[95].

Time dependence

Moderate level of urgency and treatment outcomes will not be highly affected by some days of delay.

Population in need of interventions

Treated population: Both genders, all groups. Prevalent cases of migraine will be treated, and 100% get acute treatment and 38% will be require long-term prophylaxis.

Affected population: Both genders, all groups. Prevalent cases of migraine will be affected, and 100% get benefits from acute treatment and 38% will benefit from long-term prophylaxis.

Therefore, in the analysis, prophylaxis and acute migraine attacks are treated separately.

Disease stage addressed: Migraine

Treatment is initiated when the patient has been diagnosed. Baseline disability (Dw) is 0.441 [1, 109].

Intervention effectiveness and safety

Aspirin is the most common of NSAIDs to target the acute phase of migraine attacks. A meta-analysis shows that aspirin has a disability reduction (RR) of 0,52 (95% CI 0,41 – 0,61) 2 hours after intake, and a disability reduction (RR) of 0,39 (95% CI 0,27 - 0,49 at 24 hours compared to a placebo [77]. Because of the availability of aspirin, this is chosen as the main drug of choice for the analysis, even though costs of paracetamol are cheaper and is safer in use.

Kirthi et al. [77] concluded that 50 or 100 mg of sumatriptan (second-line treatment) is also an effective drug to treat the acute phase of migraine.

Magnesium prophylaxis can be used when patients experience side effects from the first line drugs. A systematic review shows that magnesium can reduce the frequency of migraine attacks by 22-43%, however that more research on the efficacy of migraine is needed as its effects are debated [110]. For this reason, magnesium prophylaxis is omitted from further analysis.

A systematic review provides evidence for efficacy of several migraine prophylaxis drugs [111], yet for this intervention we focus on propranolol and amitriptyline in their recommended dosages (160mg, 100 mg) because these drugs are on the WHO Essential Medicines list (available on https://list.essentialmeds.org/). Topiramate (100mg) will also be included as it is supported by good evidence [61, 111]. It is estimated that 38% of patients can benefit from prophylaxis [112], and can be prescribed in the case of more than 3 attacks per month.

Table 3: Effect of interventions for migraine on disability (risk of getting better)

	Intervention effect (disability reduction)	Reference	Certainty of evidence
Acute drugs Aspirin 1000 mg Sumatriptan 50 mg Almotriptan12,5 mg	 0.39 0.35 0.45	Linde et al. (2015) [61]	High (Metaanalysis)
After 2 hours (acute drugs: aspirin)	1-0.48=0.52	Kirthy et al. (2010) [77]	High (Metaanalysis)
After 24 hours (acute drugs: aspirin)	1-0.61=0.39	Kirthy et al. (2010) [77]	High (Metaanalysis)
Prophylaxis Propranolol 160mg Amitriptyline 100mg Topiramate 100mg	 0.28 0.44 0.40	Linde et al. (2015) [61]	High (metaanalysis)

Calculations of total efficacy of acute and prophylaxis on disability:

Effect of first using acute drugs (effect 0.39) and then adding prophylaxis (average effect about 0.40) to a 38% [113] of those with multiple migraine attacks (more severe migraine):

Total: 1 - (1-0.39)*(1-0.40) = 1 – 0.61*0.60 = 1 – 0.37 = 0.63

Non-health benefits that we expect from this intervention, but that we do not model:

- Economic benefits due to increased productivity and less absenteeism in society in individuals, households and society.
- Reduction of stigma and stress upon close relatives
- Insight into own stressors and awareness of potential disease triggers
- Increased social participation
- 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 self-managed treatment of migraine terms of morbidity or disability in LLMIC settings.

Intervention Cost

The cost of the self-managed treatment of migraine primarily focuses on the drug costs, however costing of the full intervention is disaggregated into human resource costs, and drugs/supply costs. Costing for drugs is split up in costs for first-line treatment and first-line treatment combined with prophylaxis. Second line treatment is listed in the table as well for the sake of completeness, even though this analysis is not focussing on this treatment.

Human resource unit cost

The time that should be spent per health professional per patient suffering from migraine can be found in Table 4. The salaries of the health care workers can be found in table 5. The costs per minute for LIC are averaged between the salaries of Ethiopian health workers and Malawian health workers. The salaries for Zanzibar are not included as no information source was found.

Table 4: Human resource component for the self-managed treatment of migraine per year

Human resources	Minutes per visit	Number of days/visits	Total minutes
Neurologist	10	2	20
Nurses (health centre setting)	10	2	20
Community health worker	10	2	20

Table 5: Salaries health care personnel LIC / LMIC settings

	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

Drug and supply unit cost

Table 6: Drug/supply component for self-managed treatment of migraine

Drug/Supply	Number of units	Times per day	Days per case*	Units per case		Costs per case (in US$)

First line pain killers Paracetamol Aspirin	1	1	36	36		0,22 (costs based on asprin)
Second line treatment (triptans,magnesium)	1	1	36	36		-
Prophylaxis propranolol	1	1	365	365	*0.0419***	3,02

*Based on 3 attacks per month per year

** Based on MSH price guide - price per pill [83]

Table 7: 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	2,06	5,87	n/a		2,06	5,87
First line treatment	1,82	5,03	0,22		2,05	5,25
Prophylaxis	1,82	5,03	3,02		4,84	8,05

References

References included in the main reference list.

Appendix 2.3 Dementia: diagnostics-treatment and care

Authors: J. Hubbers, Ahmed S, Watkins D, Coates MM, Økland JM, Haaland ØA, Johansson KA

Date: December 12th, 2021

This evidence brief provides a summary of management of dementia, including diagnostics and follow-up care, drugs, and support of care givers, with a particular emphasis on parameters used in *FairChoices: DCP Analytics Tool* (FairChoices).

Table 1: Summary of model parameters and values used in FairChoices – DCP Analytics Tool, more details about assumptions and interventions in text after this table

Population:	All prevalent cases of dementia, both genders, all ages (Dw=0.14 in average)
Intervention	Diagnostics and follow-up care Drugs for dementia – Cholinesterase inhibitors (Donepezil, Galantamine, Rivastigmine) – SSRIs (Citalopram, Fluoxetide, Sertraline) – Antipsychotics (Aripiprazole, Risperidone, Haloperidol) Supporting dementia caregivers – 10% reduction of disability (improved HRQoL)
Comparator	No intervention
Outcome	Disability weight (health related quality of life = HRQoL)
Effect	Diagnostics: 0% effect Drugs for dementia – Cholinesterase inhibitors: 20% reduced disability (improved HRQoL) – SSRIs: 20% reduction of disability (improved HRQoL) – Antipsychotics 5% reduction of disability (improved HRQoL) Supporting dementia caregivers: 10% reduction of disability (improved HRQoL)
Unit cost**	Diagnostics: 2.1 US$ LIC; 5.9 US$ LMIC Drugs for dementia – Cholinesterase inhibitors: 624 US$ LIC; 630 US$ LMIC – SSRIs: 7.2 US$ LIC; 13.9 US$ LMIC – Antipsychotics 4.3 US$ LIC; 11.0 US$ LMIC Supporting dementia caregivers; 0.4 US$ LIC; 0.9 US$ LMIC

* Dw=disability weight, HRQoL=Health Related Quality of Life, LIC=Low Income Country, LMIC=Low-Middle Income Country

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

Description of condition and intervention

Dementia is a progressive syndrome which is characterized as a deterioration that cannot be attributed to a consequence of normal aging and interferes with the self-sufficiency of a patient in everyday life functioning. Dementia is defined as a decline or loss in cognitive functioning on more than one cognitive domain, which is typically memory and another domain, such as executive functioning, attention span, or language [43]. Dementia is an umbrella term for different types of conditions, such as the most known variants of dementia,

namely Alzheimer's disease, or vascular dementia, but dementia can also result from an underlying pathology, such as Huntington's disease, Lewy Body dementia, or Creutzfelt-Jakob disease, or as a consequence of neurocognitive conditions that are associated with HIV [114].

The cause of dementia is different in every type, but common risk factors are old age, cardiovascular risk factors (such as diabetes, high cholesterol, or heart diseases), brain injuries or genetics. As the disease progresses it leads to social behavioral changes, such as agitation, feeling more emotional, or not being able to control impulses [115].

The WHO has estimated that there are around 47.5 million people globally that suffer from a form of dementia, with an incidence of 7.7 million cases a year [115]. In Sub-Saharan Africa it was estimated that 2.13 million people were diagnosed with dementia in 2015, a number which is projected to reach 7.62 million in 2050 due to an expected increase of cases in Eastern and Central Africa, mainly resulting from an aging population [116]. Based on GBD 2019 data[1], we assume that disability weight is in average 0.14 for dementia. However, this varies by severity (Mild: 0.069; Moderate: 0.377; Severe: 0.449 [109, 117]) and since the majority of patients have mild dementia we see a low value of the average disability weight.

The global societal costs of dementia are estimated to be around $820 billion [118]. Prince et al. [56] demonstrate that the costs can be explained by direct and indirect health costs associated with dementia, such as the use of primary health care services or institutionalization, but also the costs for loss of the ability to work for the patients. The costs also include costs from family members caring for a patient, due to low productivity or absenteeism from work [55, 56].These costs add up to high financial consequences for families involved, especially in the low- and low-middle income countries (LICs/LMICs) [12, 55]. Furthermore, the expectation is that these costs will increase tremendously as a result of the increasing burden of disease due to aging populations.

Table 2: International guidelines for dementia

Organization	Guideline	Applicability in LIC & Lower MIC settings
WHO (2017)	Risk reduction of cognitive decline and dementia [119]	√
WHO (2018)	Towards a dementia plan: a WHO guide [120]	√
Alzheimer's disease international (2017)	Dementia in Sub-Saharan Africa Challenges and opportunities [121]	√

1. ***Diagnostics and follow-up primary care***

Receiving a dementia diagnosis in an early phase of the condition requires a mental, physical, and social examination. Diagnosis can be supported by neuroimaging, such as an MRI, or identifying biomarkers though cerebrospinal fluid through lumbar puncture, also known as spinal tap, although this is generally not performed in LLMIC settings [114]. Additional neuropsychological screening or testing can provide insight in the reduced function of any of the cognitive domains, such as memory, attention span or language. However, translations of diagnostic- or screening tests are not always available into the patient's native language and may therefore not always applicable to LLMIC settings. Secondly, not all neuropsychological tests have been validated in LLMICs [116]. Further problems that contribute to underdiagnosis include limited health illiteracy, limited access to health care services and lastly stigma [122].

Diagnosis in LLMICs often occurs through the process of clinical diagnosis, where health personnel base their diagnosis not on medical tests but on symptom description of the condition and daily functioning. Therefore, the diagnosis is usually made by diagnostic interviews with patient and a close family member, reviewing the medical history of the patient, neuropsychological screening, and testing. Often the indication from close family members or partners that someone can perform so-called activities of daily living (ADL) and therefore are no longer self-sufficient is indicative for dementia [116].

Dementia decline is often measured as progression on the MMSE. Early screening with the Mini Mental State Exam (MMSE) can identify individuals with dementia earlier on, and subsequently, adequate care can be provided (e.g. an nutritional checkup, weight, height, examination of vital signs or a possible early start on cholinesterase inhibitors). This often results in delayed institutionalization, which has positive effects on the health care system, family and community, however due to the limitations listed above, a timely diagnosis is not always obtainable.

Follow up and primary care of patients is important in order to assess the health status, as impaired cognition might result in not addressing other coexisting illnesses in an adequate manner. Because of the dementia, patients might not remember to take their medication, take too much medication or forget to eat and therefore lose weight or have severe nutritional deficits. An adequate follow-up can aim to prevent this by providing check-ups on a patient's health status. Primary care might also slow down vascular risk factors that can progress dementia even further [55, 56].

An American systematic review shows that patients that suffer from dementia have a better quality of life when they are still able to perform ADL-tasks, are able to perform pleasant activities, are in good health and have good mobility and mood, and naturally a preservation of cognitive functions [123]. However, studies on the quality of life in LLMICs are scarce.

In dementia care, the focus is placed on the role of prevention through improving lifestyle factors and early diagnosis. Early diagnosis provides room for better management of dementia, providing psychoeducation and support for caregivers in a sustainable way [25]. Early diagnosis could lead to reduced costs due to better management, however, early diagnosis could be a negative influence on social and psychological factors [124].

2. Drug treatment

There are no effective pharmacological treatments to prevent or treat dementia to date. Many studies have been conducted to assess the efficacy of cholinesterase inhibitors (for example, donepezil, rivastigmine or galantamine) to impede or treat Alzheimer's disease, however no evidence is available in LLMIC settings [56]. Secondly, these medications are not on the list of essential medicines. Pharmacological treatment for symptoms is sometimes given in the form of SSRIs or antipsychotica to help with the agitation, anxiety, psychosis, and behavioral symptoms that can occur in patients with dementia [25]. Risperidone and haloperidol are on the list of essential medicines. Psychological treatments or interventions are given to patients to help reduce the behavioral symptoms [125].

Baseline coverage is currently set at 5%/8% for SSRIs and antipsychotics and 0% for cholinesterase inhibitors in LIC/LMIC settings.

Dementia typically leads to a reduction of 3-4 (mean 3.5) points on the MMSE per year. Drug treatment can slow this reduction with 1 –2 (mean 1.5) points a year [126]. Hence, patients benefit from early treatment.

3. Supporting dementia caregivers

The progressive nature of the disease leads to a need for constant supervision from caregivers, and makes a dementia patient highly dependent for help on daily tasks. Caregivers are often family members, in particular the patient's children, and caregiving tasks can be shared in between members of the household. In LLMIC settings, caregiving at home is more common than professional care as the family support systems may be better, larger and more feasible [127]. It is estimated that 58% of the costs of dementia in LIC settings and 65% in middle-income countries are because of all costs related to informal care [128]. The 2010 World Alzheimer Report (2010) [129] assumes that in East Sub-Saharan Africa, informal caregivers (81% female, 41% of the cases

this equals a spouse) spend 3.6 hours per day on activity of daily living (ADL) tasks and 2.6 hours per day on supervising the dementia patient.

The term “caregiver burden” entails the physical, mental and socio-economic consequences that occur from providing care for a loved one [130]. Dementia carries a lot of stigma, that also extends to caregivers and causes stress [118].

Interventions targeting caregivers consist of psycho-education to advise about the disease and its symptoms, psychological therapy such as cognitive behavioral therapy or counseling. Interventions can serve as guidelines in care taking, caregiver support or respite (emergency) care, or a combination. Many of the caregiver interventions focus on reducing stress and depressive feelings to prevent the caregiver from being overburdened, ultimately resulting in better care for the patient [55]. Cognitive behavioural therapy has the highest impact. It is important that these programs are implemented from a horizontal, health system approach in a community program.

As dementia is not always accurately diagnosed in LLMIC settings, strategies that could lead to an improved quality of life for patient and caregiver, such as home optimization strategies in an earlier stage of dementia, are not among the possibilities. These home-modifications can postpone institutionalization and allow for as much independence in activities of daily living (ADL). However, institutionalization in LLMICs is not always a possibility either.

Not much evidence is available on caregiving in Sub-Saharan Africa, yet the limited evidence is contested, for example due to lack of randomized studies, studies in appropriate settings, or studies using flawed methodology. Results from a community-based study in the Hai district in Tanzania implied that caring for dementia patients does not carry a high burden, as the symptoms in an early phase of the disease are often attributed to the normal ageing process [123]. A follow-up study showed that taking care of patients with neurodegenerative disorders leads mild to high levels of burden for the caregivers, especially when there is no professional support, options for institutionalization, or limited money and resources [118]. Providing care for dementia patients impacts the quality of life of both the patient and the caregiver and increases direct and indirect household-related costs because of medical expenses or missing out on income as a result of absenteeism from work [55].

In a randomized controlled trial [131], a multicomponent intervention was assessed in White/Caucasian, Hispanic/Latino, or Black/Afro-American caregivers of dementia and Parkinson patients when compared to a control group. The results show that the intervention, that focused on depression, care burden, social support, self-care and patient problem behaviours, improves the quality of life of caregivers for the white/Caucasian group and the Hispanic/Latino groups only. In the black/Afro American group a significant increase in Health-Related Quality of Life (HRQoL) was observed when the caregivers were the patient’s spouse (results in table 3). However, the limitations to this study are that there is a the relatively short (6-month, one time only) follow-up period and it is focused on differences in the USA only.

Table 3: HRQoL impact of having family/spouse as caregiver.

White/Caucasian	Coeff, -0.2 (CI, -0.4 to 0.0)	P<0.032
Hispanic/Latino	Coeff, -0.3 (95%CI, -0.5 to -0.1)	P<0.001
Black/African-American	Coeff, -0.1 (CI, -0.3 to 0.1)	P=0.23
Black/African-American intervention x spouse interaction	-0.5 (CI, -0.9 to –0.1)	P=0.008

In a systematic review, the authors compiled a list of 10 themes that came up during qualitative analysis to estimate which factors that matter the most with respect to the quality of life for caregivers of dementia patients [132]:

1. Demographics

2. Carer emotional wellbeing
3. Carer-patient relationship
4. Support received
5. Dementia characteristics
6. Carer independance
7. Demands of caring
8. Carer self-efficacy
9. Carer health
10. Future

A qualitative study in Uganda describes the impact of caring on informal caregivers that extends to a physical, financial and social burden [133]. The recommendations are to provide and extend support services, such as groups, counselling options, and campaigns targeting knowledge on dementia, reducing stigma and creating a better understanding of the caregiver burden.

Baseline coverage for interventions targeting caregivers is currently set to 5%/8% for LIC/LMIC settings in FairChoices as health care workers are assumed to not be aware of this intervention.

Type of interventions

1. Diagnostic, 2. chronic management care, 3. health promotion

Delivery platform

1. Hospital, 2. Hospital/health centres, 3. community

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 [95].

Time dependence

Moderate level of urgency and treatment outcomes will not be highly affected by some days of delay.

Population in need of interventions

All prevalent cases would benefit from diagnosis of dementia and follow-up care.

All individuals diagnosed with dementia from psychiatric symptoms can benefit from drug treatment with antipsychotics.

The caregiver intervention is targeted at all caregivers that take care of a dementia patient. This benefits both the caregivers as well as the dementia patients.

Disease stage addressed

The disease stage addressed is the moment of diagnosis of dementia, which is often assessed when the patient has reached a level of reduced self-sufficiency, and the care patients receive afterwards. For drug treatment, Treatment is initiated in diagnosed individuals, or after experiencing psychiatric symptoms that can occur with dementia. GBD condition *"Alzheimer's disease and other dementias"* is used to match with country specific epi data input.

Intervention effectiveness and safety

1. Diagnostics and follow-up: Patients experience no direct health benefit from a dementia diagnosis, but it comes at a cost. During follow up, patients receive weight, height and blood pressure measurements. However, dementia diagnosis is treated as a prerequisite for further interventions. Baseline coverage set at 5% in LIC and 8% in LMIC setting.
2. Drug treatment: The effects of the cholinesterase inhibitors donepezil, rivastigmine, and galantamine will be assessed, as well as the antipsychotic drug risperidone. Baseline coverage is currently set at 5%/8% for antipsychotics, 25% for SSRIs and 0% for cholinesterase inhibitors in LIC/LMIC settings.
3. Supporting caregivers: Baseline coverage is currently set at 5%/8% in LIC/LMIC settings. If community health workers are not aware of the condition, caregivers currently receive no support.

Cholinesterase inhibitors

The cholinesterase inhibitors in this model were selected by selecting the ones that are most frequently assessed in literature reviews and meta-analyses and have proven to show a degree of efficacy as well as are considered safe.

Antipsychotics

Antipsychotics are sometimes used in the treatment of dementia as a last resort type of drug treatment. However, as they pose many side effects and have a small effect size in general, they should be considered last in the pharmacological treatment. The drugs haloperidol, aripiprazole and risperidone are listed below. Other antipsychotics, like olanzapine and quetiapine were excluded as their effectivity and safety does not surpass the effects of the previously mentioned options. A meta-analysis of antipsychotics shows that aripiprazole is associated with improvement of NPI, BPRS and CMAI scores and is safer, compared to risperidone [134].

SSRIS

To treat the behavioural symptoms of dementia, SSRIs can be used. Popular choices are citalopram, fluoxetide and sertaline. In this model we use Fluoxetide and sertaline, as no costing information was avalable for citalopram.

Supporting caregivers

Determining the effectiveness of caregiver interventions is complex as this has an effect on both the patients and caregivers simultaneously. Outcomes for the caregivers however, are mainly non-health benefits for the caregivers, such as outcomes in quality of life, and depends on the disease stage. Indirect benefits for caregivers are not analysed in FairChoices. The quality of life for the caregivers will indirectly affect the patients and the effect measure was set to 5% reduction of disability weight of the patient (assumption, no evidence identified).

A summary of the assumed health effects of the dementia interventions (with detailed overview of findings from literature and rationale for these assumptions are provided in table 4):

Diagnostics: 0% effect

Drugs for dementia

– Cholinesterase inhibitors: 20% reduction of disability / improvement of HRQoL

– SSRIs: 20% reduction of disability / improvement of HRQoL

– Antipsychotics 5% reduction of disability / improvement of HRQoL

Supporting dementia caregivers – 5% reduction of disability / improvement of HRQoL

Table 4: Population and effectiveness of interventions for dementia

Category	Model parameter	Notes
Treated population Gender Age	All patients All caregivers Both 60-99 18-99	 For dementia patients For dementia caregivers
Affected Population	Prevalent cases	
Intervention	Drug treatment for dementia patients	Both disease moderators & antipsychotics
Comparison	Placebo	
Baseline disability dementia	Mild: 0.069 Moderate: 0.377 Severe: 0.449	Neumann et al. 1999 [117]
Mortality Reduction (RRR)	Not reported	
Disability Reduction (RRR) of atypical antipsychotics	Between -0,32 / -1,84	Based on improved performance on 4 different rating scales compared to placebo (Ma et al., 2014 [135])
Diagnosis and follow up	0	Assumed 0 due to no direct health benefits
Cholinesterase inhibitors		
Donepezil	NPI Mean difference –1,45 95% CI –2,70 to –0,20 MMSE: Mean difference 1.05, 95% CI 0.73 to 1.37	Jin & Liu, 2019 [79] After 26 weeks the drug is associated with better cognitive outcomes compared to a placebo (Birks et al., 2018) [78]
Galantamine	NPI Mean difference –1,80 95% CI –3,29 to –0,32 Placebo: -2,14 (4,34) Drug: -1,41 (4,05)	Jin & Liu, 2019 [79] Worsening on MMSE in 24 months: P<0,001 (Hager et al., 2014) [136]

Rivastigmine	NPI Mean difference –1,09 95% CI –2,89 to 0,67 (not significant!) MMSE: Mean difference 0.74, 95% CI 0,52 to 0,97	After 26 weeks the drug is associated with better cognitive outcomes compared to placebo (Birks et al., 2015) [137]
Antipsychotics		
Aripiprazole	NPI Mean difference –3,65 95% CI –6,92 to –0,42 NPI: standardized mean difference-0,17, 95% CI –0,31 to –0,02 BPRS: standardized mean difference 0,20 95% CI –0,35 to –0,05 CMAI standardized mean difference -0,30 95% CI –0,55 to- -0,05	Jin & Liu, 2019 [79] Based on scores compared to placebo (Yunusa et al., 2019) [134] Standardized mean difference <0,4 small effect size
Risperidone	NPI Mean difference –3,20 95% CI –6,08 to –0,31 CMAI standardized mean difference -0,26 95% CI –0,37 to- -0,15	Jin & Liu, 2019 [79] Compared to scores with placebo (Yunusa et al., 2019) [134]
Haloperidol	NPI Mean difference –3,44 95% CI –7,39 to –0,40	Jin & Liu, 2019 [79]
Atypical antidepressants (SSRIs)		
Citalopram	mean difference MD, -0.89, 95% CI, -1.22 to -0.57	Agitation only - no costing information available
Fluoxetide	MMSE MD = 1.16, 95% CI: 0.41–1.90, P = 0.002	Xie et al., 2019 [80]
Sertraline		No costing information available
Caregivers of dementia patients		
Effect caregivers	No studies identified	Assumed to have similar efficacy as antipsychotics

Effectiveness Cholinesterase inhibitors

MMSE mean difference score

The effectiveness of cholinesterase inhibitors is measured on by reduction of points on the screening test Mini Mental State Exam (MMSE). The test has a maximum of 30 points that equals full, unimpaired cognition. A score between 25-30 would therefore be seen as no cognitive impairment. A score of 21-24 points can indicate mild cognitive impairment/mild dementia, between 10-20 points would equivalate moderate dementia and 9 or less points towards severe cognitive impairment. To determine the efficacy of the drugs, the following disability weights were used[109]:

Dementia: non 0.0 MMSE 25-30

Dementia: mild 0.069 (0.046-0.099)
MMSE 21-24

Dementia: moderate 0.377 (0.252-0.508)
MMSE 10-20

Dementia: severe 0.449 (0.304-0.595)

MMSE <9

Henceforth it was calculated that 1 point difference on the MMSE corresponds to 0.45/(25-9)=0.028 in added disability.

Effectiveness antipsychotic effects based on NPI scores
NPI mean difference score

The Neuropsychiatric Inventory (NPI) was developed to screen behavior (such as agitation, hallucinations, sleep or anxiety) on the dementia spectrum and is to be filled out by the caregivers of a dementia patient. A sum score is given between by adding the 10 domain scores and ranges between 0-144 points. If the caregiver provides a positive answer on any of the behaviours, they are asked to score both the intensity and frequency on a score from 1-4. The multiplication of the intensity and frequency scores equals the domain score.

Non-health benefits:

These interventions are important because dementia treatment includes individual benefits, yet also provides benefits in broader perspective towards family members and society.

Diagnosis:

- More clinical benefits though timely treatment can improve the quality of life of patients and families
- Early diagnosis can provide for a good overview of future perspective.
- Patients have the right to know their diagnosis (ethically)
- Increased knowledge on disease through increased awareness early on

Drug treatment:

- Delay in clinical symptoms results in less burden for health personnel
- Improved quality of care resulting from disease burden
- Delayed institutionalization
- Higher patient quality of life
- Higher quality of life for family members
- More societal participation
- Longer stable productivity of family members during the delay
- Lower indirect costs associated with the disease

Caregivers:

- Reduction of caregivers stress
- Increased productivity if caretaking becomes less demanding, resulting in an increased income
- Increased quality of life for patients
- Less strain on the workforce as patients require less professional help
- Consequences for social participation
- Increased perceived life control

Need for future research

Long term-controlled design studies with sufficient power and follow-up period needed to estimate the effect of dementia interventions.

Intervention Cost

For an elaborate explanation of the interventions, see description of condition and interventions.

Human resource unit cost

The time that should be spent per health professional per patient suffering from dementia, including the estimated time health care professionals spend on caregivers can be found in Table 5. The salaries of the health care workers can be found in table 6. The costs per minute for LIC are averaged between the salaries of Ethiopian health workers and Malawian health workers.

Table 5: Human resource component for the dementia interventions

Human resources	Number of visits	Time per visit (minutes)	Total time per case
Diagnosis			
Neurologist	1	30	30
Nurse	1	10	10
Follow up			
Neurologist	3	15	45
Nurse	3	10	30
Drug treatment			
Neurologist	4	10	40
Nurse	4	15	60
Supporting caregivers of dementia patients			
Community health worker	3	15	45

Table 6: Salaries health care personnel LIC / LMIC settings

	Cost per minute Ethiopia	Cost per minute Malawi	Cost per minute Tanzania	Cost per minute LIC (average)	Cost per minute LMIC (Tanzania)
Neurologist	0,060	0,064	0,178	0,062	0,178

Pharmacists	0,024	0,028	0,070	0,026	0,070
Medical doctor	0,047	0,044	0,131	0,045	0,131
Nurse	0,019	0,020	0,054	0,020	0,054
Community health worker	0,014	0,005	0,020	0,010	0,020
Physical therapist	0,029	0,033	0,097	0,031	0,097
Clinical health officer	0,014	0,016	0,038	0,015	0,038

Drug and supply unit cost

The cost of the dementia interventions primarily focuses on the drug costs, however costing of the full intervention is disaggregated into human resource costs, and drugs/supply costs. Costing for drugs is split up in costs for cholinesterase inhibitors, SSRIs and antipsychotics. Cholinesterase inhibitors are the golden standard. Antipsychotics should only be considered if there are no other alternatives to treat behavioral symptoms of dementia.

Table 7: Drug/supply component for dementia treatment

Drug/Supply	Number of units	Times per day	Days per case	Units per case	Price per pill (in US$)	Cost per case (in US$)
Cholinesterase inhibitors	1	1	365	1	1,7	620,5
SSRI	1	1	365	1	0,0096	3,5
Antipsychotics	1	1	42	1	0,0157	0,66

*Estimated from MSH price guide [83]

Table 8: Total unit costs LIC/LMIC

	Total HR Costs LIC(in US$)	Total HR Costs LMIC (in US$)	Total drug costs (in US$)	Other costs	Total costs LIC (in US$)	Total costs LMIC (in US$)
Diagnosis	2,05	5,87	n/a		2,05	5,87
Drug treatment (Cholinesterase inhibitors)	3,65	10,34	620,5		624,15	630,84
Drug treatment (SSRIs)	3,65	10,34	3,5		7,16	13,85
Drug treatment (antipsychotics)	3,65	10,34	0,66		4,31	11,0
Caregivers of dementia patients	0,43	0,9	n/a		0,43	0,9

References

References included in the main reference list.

Appendix 2.4 Parkinson's disease

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Date: December 9th, 2021

Model assumptions

Table 1: Summary of model parameters and values used for management of Parkinsons's disease in FairChoices – DCP Analytics Tool

Population:	All prevalent cases of parkinson, both genders, all ages (Dw=0.15 in average untreated)
Intervention	– Diagnostics of Parkinson's disease – Drug treatment – Physical therapy, basic – Physical therapy, extensive
Comparator	No intervention
Outcome	Disability weight (health related quality of life)
Effect	– Diagnostics of Parkinson's disease: 0% effect – Drug treatment: 70% reduction of disability or improvement of HRQoL – Physical therapy, basic: 5% reduction of disability or improvement of HRQoL – Physical therapy, extensive: 10% reduction of disability or improvement of HRQoL
Unit cost*	Diagnostics: 2.1 US$ LIC; 5.9 US$ LMIC Drugs: 82.7 US$ LIC; 88.2 US$ LMIC Physical therapy, basic: 1.9 US$ LIC; 5.8 US$ LMIC Physical therapy, extensive: 5.6 US$ LIC; 17.4 US$ LMIC

HRQoL= Health Related Quality of Life

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

Description of condition and intervention

The management of Parkinson's disease, including drug treatment, surgery and physiotherapy.

Intervention Parkinson 1	Parkinson's drug treatment (levodopa/carbidopa)
Intervention Parkinson 2	Parkinson's disease surgery (pallidotomy, thalamotomy, DBS)
Intervention Parkinson 3	Physical therapy for Parkinson's patients

About Parkinson's disease

Parkinson's disease is a neurodegenerative disease that presents in motor symptoms such as tremor, rigitidy of the muscles, bradykinesia (slowness or absence of spontaneous movements) or gait- and balance problems. Because of the many motor symptoms affected, Parkinson's disease is categorized as a movement disorder. [138]Although the pathways of developing Parkinson's disease are not yet clear, and many origins are plausible, the result is a degenerative process in the basal ganglia of the brain, called the substantia nigra, responsible for dopamine production. Therefore, Parkinson's disease is resulting in reduced dopamine levels, that affect and impair movement [139]. The onset of Parkinson's disease occurs most often around 60 years of age, and deterioration is slow, on average around 10/15 years.

Diagnosis

Parkinson's disease is frequently underdiagnosed. Diagnosis of Parkinson's disease is often based on the clinical presentation of symptoms, as MRI or lumbar punctions or other type of biomarkers are not always an option in low-and low-middle income countries. Clinical tests such as the Movement Disorder Society – Unified Parkinson's Disease Rating Scale can be used to assess symptoms. The MDS-UPDRS is a test that consists of 4 parts: 1. Mentation, Behavior, and Mood 2. Activities of daily life 3. motor symptoms 4. Modified Hoehn and Yahr Scale, and 5) Schwab and England ADL scale. The maximum score of 199 indicating the worst score on all segments, the minimum score is 0. For physiotherapy, part 3: motor symptoms is the most important subscale, with a maximum of 132 points [140, 141].

In cases where tremor presents as the main symptom, Parkinson's disease is relatively easily recognizable. However, there is a treatment gap for Parkinson's disease, as it is not always recognized in the community due

to a lack of awareness. Parkinson's disease is highly associated with witchcraft or stigma, and often treatment is sought with natural healers, maintaining the treatment gap. Further issues are the lack of resources, funding and adequately trained health personnel.

Treatment of Parkinson's disease

Parkinson's disease can be managed with drugs that aim improve movement, for example by substituting the body's dopamine deficiency with Levodopa. Parkinson's disease can be treated by dopamine agonists, as well as levodopa. The golden standard in drug therapy is combining levodopa with carbidopa. Levodopa is converted to dopamine in the brain, whereas carbidopa prevents the breakdown of levodopa in the body, resulting in a higher concentration of levodopa in the brain. Within the early phase of the disease, between 0-5 years after diagnosis, around 70% of patients start up with a dopamine agonist or levodopa, and after 5-8 years all Parkinson's patients require drug treatment.

However, no effective treatment is available that can halt the progression of Parkinson's disease. Despite the initial positive effectivity of drug treatment on Parkinson's disease (the so-called honeymoon phase), due to the progressive nature of the disease, effectivity of the drugs is reducing over time. This is also defined as the OFF-state, the state in which medication wears-off. Over time, Parkinson's patients spend more time in an OFF-state. Furthermore, drug treatment needs to be revised often due to the side effects. Side effects of the medication include nausea, excessive movements (dyskinesia), and hallucinations[140, 142].

It is possible to perform surgery on patients that suffer from Parkinson's disease to treat the symptoms associated with the disease, particularly the motor symptoms associated with the disease. This is often done as a last possible option, when the effects of drug therapy are reduced. Three types of surgery are available out of which deep brain stimulation (DBS) is the most used, where electrodes are inserted in the brain (subthalamic nucleus, globus pallidus or the thalamus) in order to send out electrical pulses that help the connections in the brain [143].

More accessible is physiotherapy. A meta-analysis provides evidence that different types of physiotherapy and physical activity can reduce motor symptoms, balance and improve gait and quality of life in Parkinson's disease patients. Physiotherapy consequently can lead to a reduction on the MDS-UPDRS part 3: motor symptoms[82]. However, due to the progressive nature of Parkinson's disease, the efficacy of physiotherapy goes down when the Hoehn and Yahr score goes up. Despite learning the tools that patients can apply themselves, over time the effects of physiotherapy decline.

Socio-economic burden of Parkinson's disease in LLMICs

As the number of Parkinson's patients is rising, so are the socio-economic costs and burden (see table 2) accompanied with the disease. Parkinson's patients retire early due to their symptoms, resulting in a loss in productivity both for the individuals and society. Furthermore, as the disease can result in high disability and premature death, caregivers play an important role, causing loss of production in this group as well. In the USA alone, the direct and indirect costs of Parkinson's disease add up to $26,5 billion in 2017, a number that will only go up as the prevalence goes up[144].

Table 2: Baseline characteristics of Parkinson's disease (source: GBD results tool 2019)

Mortality (number of estimated annual deaths) Globally Low SDI socio-demographic index (SDI) Low-middle socio-demographic index (SDI) Easter Sub-Saharan Africa	 363 000 211 000 23 000 4 000 4 600
DALYs lost annually Globally Eastern Sub-Saharan Africa	 3.2 million 6,292,616
Prevalence (global) Prevalence (Eastern Sub-Saharan Africa)	8,511,022 77,829
Incidence (global) Incidence (Eastern Sub-Saharan Africa)	1,081,723 10,664

Table 3: International guidelines for Parkinson's disease

Organization	Guidelines for Parkinson's disease	Applicability in LIC & Lower MIC settings
Royal College of Physicians: National Collaborating Centre for Chronic Conditions (UK)	Parkinson's Disease: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. London: Royal College of Physicians (UK); 2006. PMID: 21089238.	Limited
International Parkinson and Movement Disorder Society	Update on Treatments for Nonmotor Symptoms of Parkinson's Disease—An Evidence-Based Medicine Review (2019)	Limited
International Parkinson and Movement Disorder Society	Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease (2018) [145]	Limited

Intervention attributes

Type of interventions

Chronic management care

Delivery platform

Hospital level.

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 [95].

Time dependence

Moderate level of urgency and treatment outcomes will not be highly affected by some days of delay.

Population in need of interventions

All individuals diagnosed with Parkinson's disease.

Disease stage addressed

Disease stage is assumed to be post-diagnosis in order estimate adequate disease management. *Disability weights[109]:* Mild 0.010; Moderate 0.267; Severe 0.575.

Intervention effectiveness and safety

See description of condition and intervention for more information regarding the interventions included in this evidence brief.

Model assumptions

Table 4: Summary of model parameters and values used in FairChoices – DCP Analytical Tool

Category	Model parameter	Notes
Treated population	All	
Gender	Both	
Age	All ages	

Affected Population	Prevalent cases	
Baseline disability	Mild: 0.010 Moderate 0.267 Severe 0.575	
Mortality Reduction (RRR)	Not applicable	
Disability Reduction (RRR) Drug therapy(Levodopa, Carbidopa, Selegiline, Ropinirole, Rotigotine)	50-80%	Based on 10 years, Zhuo et al., 2017 [81]
Levodopa/carbidopa (Sinemet)	Mild (0-5 years): 80% effective Moderate (5-9 years): 30% effective Severe (9+ years): 8% effective	Based on expert opinion. Years after diagnosis.
Prevalence according to state	Mild: 100/(100+95+80) = 0.36 Moderate: 95/(100+95+80) = 0.35 Severe: 80/(100+95+80) = 0.29	Assume 5% die in the first 5 years (~baseline mortality in mild period). Assume 15% die in the next 4 years (moderate period) Assume 80% die later (severe period)
Disability Reduction (reduction of total UPDRS scores) Surgery (DBS) Disability reduction (reduction of UPDRS part 3. Motor symptoms) Surgery (DBS) in ON-phase Disability reduction (reduction of UPDRS part 3. Motor symptoms) Surgery (DBS) in OFF-phase	-5.14 (-6.18, -4.10); P < 0.00001) SMD 1.63 (95% CI: 0.28–2.98) SMD 3.43 (95% CI: 0.04–6.89, p < 0.01)	Compared to best medical therapy, reduction on UPDRS total score. Bratsos et al., 2018 [143] Mao et al., 2019 [146] Mao et al., 2019 [146]
Disability Reduction Physiotherapy	(MDS)-UPDRS (n = 26; SMD 0.48, 95% CI 0.35 to 0.60, P < .001)	Radder et al., 2020 [82]
Prevalence Reduction (RRR)	Not applicable	
Incidence Reduction	Not applicable	
Fertility Reduction	Not applicable	

A study assessing the minimal clinical important differences (CID) on the UPDRS scores indicate the following scores[147]:
Improvement: −3.25 points minimal, but clinically significant decrease in UPDRS scores
Worsening: - 4.63 points minimal, but clinically significant increase in UPDRS scores.

Non health benefits:

- Treatment of motor symptoms can lead to less stigmatization as the disease symptoms are not that obvious
- Increased productivity in work or school work, impacting the whole family and society
- Diagnosis can lead to more awareness of the disease and result in more social participation
- Treatment of Parkinson's disease can remain a patient's independence in ADL, depending less on their family as well as the health care system.

Need for future research
Long term-controlled design studies with sufficient power and follow-up period needed to estimate the effects of management on mortality and morbidity, disability, incidence/prevalence of Parkinson's disease in LLMICs.

Intervention Cost

The cost of the self-managed treatment of Parkinson's disease primarily focuses on the drug costs, however costing of the full intervention is disaggregated into human resource costs, and drugs/supply costs. Costing for

drugs is based on Levodopa/Carbidopa, 4x daily. The dosage of Levodopa/Carbidopa varies widely throughout the disease progress and from individual to individual. The first phase, a lower dosage is used (on average around 200mg) and can be maximized until 1000 mg in a later phase. Costing for the surgery intervention is not plotted, as currently there are no neurosurgeons that can perform this surgery. The costs for a deep brain stimulation in India are estimated between $10.000 to 20.000. The costs for physical therapy are based on the HR costs for physical therapists in a LIC/LMIC setting.

Human resource unit cost

The time that should be spent per health professional per patient suffering from Parkinson's disease can be found in Table 5. The salaries of the health care workers can be found in table 6. The costs per minute for LIC are averaged between the salaries of Ethiopian health workers and Malawian health workers. The salaries for Zanzibar are not included as no information source was found.

Table 5: Human resource component for treatment of Parkinson`s disease patients (anually)

Human resources	Number of outpatient visits	Number of minutes per visit	Total minutes
Diagnosis			
Neurologist	1	30	30
Nurse	1	10	10
Drug treatment			
Neurologist	4	10	40
Nurse	4	15	60
Surgery			
Physical therapy (basic)	2	30	60
Physical therapy (extensive)	6	30	180

Table 6: Salaries health care personnel LIC / LMIC settings

	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

Drug and supply unit cost

Table 7: Drug/supply component for levodopa

Drug/Supply	Number of units	Times per day	Days per case	Units per case	Drug/supply unit cost (in US$)	Costs per case (in US$)
Levodopa/carbidopa (100mg/25mg)	1	4	365	1460	0,0546	79,72

Table 8: Total unit costs

	Total HR Costs LIC(in US$)	Total HR Costs LMIC (in US$)	Total drug costs [83]	Other costs	Total costs LIC	Total costs LMIC
Diagnosis	2,06	5,87	n/a	n/a	2,06	5,87
Drug treatment	2,98	8,49	79,72	n/a	82,7	88,2
Physical therapy basic	1,85	5,8	n/a	n/a	1,85	5,8
Physical therapy extensive	5,56	17,39	n/a	n/a	5,56	17,39

References

References included in the main reference list.

Appendix 3. An glance of FairChoices – DCP Analytics Tool for neurological disorders

This thesis is based on the data from BCEPS' FairChoices – DCP Analytics Tool, a web-based decision support tool in policy making, which was developed as a collaborative effort between the University of Washington, University of Bergen, and Harvard University[47]. FairChoices facilitates priority setting across multiple interventions, and analyses costs and benefits for interventions and packages of interventions.

For all interventions, the evidence briefs form the basis of the input in FairChoices, that enables users to access information about key input variables across a range of areas such as epidemiology, demography, efficacy, and cost. FairChoices ranks all interventions according to cost-effectiveness, and allows for the construction of a health benefit package based on a pre-determined budget, which provides decision makers with information on which interventions can be implemented to maximize health within the budget, but also allows for priority setting using other parameters than cost-effectiveness, such as financial risk protection, severity of disease, and political feasibility. Decision makers can assess with just a glance which interventions they can afford, and with how much their health budget needs to be raised *per capita* to afford an additional intervention.

An impression of operating FairChoices can be seen in figure 3. Proceeding by clicking any of the nodes will provide the outcomes described in the paper and its supplementary files.

Figure 3: An impression of FairChoices