Chapter 5

Neurological Disorders

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INTRODUCTION

Neurological disorders pose a large burden on worldwide health. The most recent estimates show that the neurological disorders included in the Global Burden of Disease (GBD) Study–Alzheimer's and other dementias, Parkinson's disease, multiple sclerosis, epilepsy, and headache disorders (migraine, tension-type headache [TTH], and medication-overuse headache [MOH])–represent 3 percent of the worldwide burden of disease. Although this is a seemingly small overall percentage, dementia, epilepsy, migraine, and stroke rank in the top 50 causes of disability-adjusted life years (DALYs) (Murray and others 2012).

Migraine and epilepsy represent one-third and one-fourth of this neurological burden, respectively (Murray and others 2012), and dementia and Parkinson's disease are among the top 15 conditions with the most substantial increase in burden in the past decade. In 2010, neurological disorders constituted 5.5 percent of years lived with disability (YLDs), or 42.9 million YLDs; migraine, epilepsy, and dementia were among the top 25 causes of YLDs. Migraine leads the list of neurological disorders, representing more than 50 percent of neurological YLDs or 2.9 percent of global YLDs; epilepsy represents 1.1 percent of global YLDs (Vos and others 2012).

The neurological burden of disease is expected to grow exponentially in low- and middle-income countries (LMICs) in the next decade (Murray and others 2012). Despite the significant impact of neurological disorders on patients and societies, knowledge of their epidemiology, including variation in disease frequency across place and time and understanding of associated risk factors and outcomes, remains limited, particularly in LMICs. Patients with neurological disorders often require significant social and economic support because of physical, cognitive, and psychosocial limitations (WHO 2006). Despite the high prevalence of disability, there is increasing recognition that services and resources are disproportionately scarce, especially in LMICs (WHO 2004). In addition, knowledge of the cost-effectiveness of interventions to improve neurological care in these settings remains limited.

This chapter addresses three neurological disorders: epilepsy, dementia, and headache disorders. The chapter reviews current knowledge of the epidemiology, risk factors, and cost-effective interventions for these conditions. The focus is on interventions that provide meaningful reduction in the burden to the global population, with particular emphasis on applicability to LMICs. Neurological disorders are an emerging challenge to health care systems globally, requiring further study, government and social engagement, and improvements in health care infrastructure.

This chapter uses the World Health Organization (WHO) regions—African, the Americas, Eastern Mediterranean, European, South-East Asia, and Western Pacific—to describe the global burden of the highlighted neurological disorders.

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EPILEPSY

Definitions

Epilepsy is a brain disorder traditionally defined as the occurrence of two unprovoked seizures occurring more than 24 hours apart with an enduring predisposition to generate further seizures (Fisher and others 2014). In 2014, the International League against Epilepsy provided an enhanced definition of epilepsy (box 5.1).

Epilepsy is considered to be resolved if a person has an age-dependent syndrome that is now beyond the expected age for this syndrome, or if the individual remained seizure free for the past 10 years and was off anti-epileptic drugs for at least the past five years (Fisher and others 2014). Those who continue to have seizures despite an adequate trial of a regimen of two tolerated and appropriately chosen anti-epileptic drugs (AEDs), whether in monotherapy or polytherapy, are considered to be drug resistant. Epilepsy can be classified in three categories:

- Structural or metabolic epilepsies, for example, epilepsy caused by a remote stroke
- Epilepsies of genetic or presumed genetic origin, for example, juvenile myoclonic epilepsy
- Epilepsies of unknown causes (Berg and others 2010).

Examples of more common causes of epilepsy include brain tumors, infectious diseases, brain injury, stroke, and hippocampal sclerosis. Less frequent causes include genetic causes, autoimmune causes, and malformations of cortical development (Bhalla and others 2011). Perinatal and infection-related etiologies often predominate in LMICs.

Box 5.1

Definition of Epilepsy

A person has epilepsy if he or she meets any of the following criteria (Fisher and others 2014):

- At least two unprovoked (or reflex) seizures occurring more than 24 hours apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60 percent) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome.

Epidemiology and Burden of Disease

A worldwide systematic review of prevalence has not yet been published; in general, the prevalence in door-to-door studies has been reported to range from 2.2 per 1,000 to 41.0 per 1,000 persons, often with higher estimates in LMICs (Banerjee, Filippi, and Allen Hauser 2009; Benamer and Grosset 2009; Burneo, Tellez-Zenteno, and Wiebe 2005; Forsgren and others 2005; Mac and others 2007). The median incidence per 100,000 per year is higher in LMICs at 81.7 (interquartile range (IQR) 28.0-239.5) compared with HICs at 45.0 (IQR 30.3-66.7) (Ngugi and others 2011).

The higher estimates of prevalence or incidence rates reported in many LMICs are thought to be caused by the occurrence of endemic conditions, such as malaria or neurocysticercosis; the higher incidence of road traffic injuries; birth-related injuries; and variations in medical infrastructure, availability of preventative health programs, and accessible care. In HICs, the prevalence of epilepsy is stable until after age 50, when it increases; in contrast, the prevalence in LMICs tends to be stable in the third and fourth decade of life, drops in the fifth decade, and, in some studies, increases again after age 60 (Banerjee, Filippi, and Allen Hauser 2009).

Epilepsy is associated with premature mortality, with the highest standardized mortality ratio encountered in the first year or two after diagnosis (Neligan and others 2010). In general, the standardized mortality ratio for epilepsy is approximately 3 (Hitiris and others 2007). The epidemiology of premature mortality is particularly relevant in LMICs, where 85 percent of those with epilepsy live and where the risk of premature mortality is highest (Diop and others 2005; Jette and Trevathan 2014; Newton and Garcia 2012). Most concerning is the fact that a greater proportion of deaths in LMICs are potentially preventable, such as falls, drowning, burns, and status epilepticus (Diop and others 2005; Jette and Trevathan 2014). For example, 38 percent of all epilepsy-related deaths in a large cohort of people with convulsive epilepsy in rural Kenya were caused by status epilepticus (Ngugi and others 2014). Status epilepticus is defined as ongoing seizure activity lasting five minutes or more, or two or more seizures without recovery of consciousness in between (Lowenstein and others 2001). This is an important definition, as evidence suggests that seizures lasting more than five minutes are unlikely to self-terminate. Other common causes of premature mortality in those with epilepsy include acute symptomatic disorders (for example, brain tumor or stroke), sudden unexpected death in epilepsy, suicide, and accidents (Hitiris and others 2007).

Epilepsy ranks as the 36th leading cause of DALYs globally, according to the GBD 2010 report. Epilepsy ranks as high as the 14th leading cause of DALYs in western Sub-Saharan Africa. Epilepsy ranks as the 20th leading cause of YLDs globally, second only to migraine for brain disorders (Vos and others 2012). Importantly, models in the GBD 2010 report that calculate the global burden of epilepsy consider only the previously termed idiopathic/cryptogenic epilepsy and not epilepsy secondary to causes such as infections, stroke, or genetic syndromes, which may be responsible for more than 50 percent of the deaths in these regions (Murray and other 2012). Therefore, the data likely underrepresent the true burden of epilepsy, especially in LMICs.

Interventions

Population-Based Interventions

Targeting Epilepsy Risk Factors. Although genetic causes of epilepsy cannot be prevented, the more common structural or metabolic causes can be the target of primary prevention through public health policies. For example, helmet use for motorcyclists and laws against drinking and driving can reduce the risk of traumatic brain injury, a common risk factor. Improved perinatal care, particularly in rural areas, can reduce the incidence and subsequent prevalence of epilepsy. In one Tanzanian community-based, case-control study, adverse perinatal events were present in 14 percent of children with epilepsy but absent in all controls (Burton and others 2012). A population-based cross-sectional and case-control study in Ghana, Kenya, South Africa, Tanzania, and Uganda reported an association between abnormal antenatal period and active convulsive epilepsy (Ngugi and others 2013). Although abnormal delivery and home delivery did not reach statistical significance, there was a trend for these to be associated with active convulsive epilepsy.

Policies to control neurocysticercosis, a common risk factor in LMICs, would be an effective way to reduce epilepsy worldwide. An extensive eight-year public health and educational intervention program aimed at reducing symptomatic epilepsies (particularly those caused by perinatal insults and neurocysticercosis) was implemented in rural Salama, Honduras, starting in 1997 (Medina and others 2011). The program included education and media campaigns, animal husbandry training for pig farmers, construction of water projects and proper sewage disposal, deworming of school students, ongoing taeniasis surveillance, and other initiatives (Medina and others 2011). The proportion of epilepsy caused by neurocysticercosis was reduced from 36.9 percent in 1997 to 13.9 percent in 2005 (Medina and others 2011). The overall cost of this study was US$1.33 million, although an economic analysis was not conducted to determine if it was cost-effective.

A smaller-scale study examined the efficacy of teaching methods to prevent epilepsy caused by neurocysticercosis in western Kenya (Wohlgemut and others 2010). The authors found that knowledge improved significantly using this teaching method. Whether this program reduced the incidence of epilepsy caused by taenia solium was not examined, but the findings represent a positive step. The expert consultation report on foodborne infections, such as taeniasis/cysticercosis, proposes some approaches to ensure sustainable prevention and control of this often endemic agent. These approaches are listed in box 5.2; however, the report did not define the costs of implementing these approaches (WHO 2011).

Anti-Stigma Interventions. Civil rights violations, such as unequal access to health and life insurance or prejudicial weighting of health insurance provisions, are common. Discrimination in the workplace and restricted access to education are frequent. School teachers often have poor knowledge and negative attitudes toward children with seizure disorders (Akpan, Ikpeme, and Utuk 2013). Stigma is associated with social and economic consequences. Persons with epilepsy may not seek treatment or convey related health concerns to their care providers, further widening the treatment gap.

Improved knowledge about epilepsy is associated with positive attitudes and reduced stigma, but the

Box 5.2

Approaches to Ensure Sustainable Prevention and Control of Neurocysticercosis

- Preventive chemotherapy of human taeniasis through mass or targeted treatment of humans
- Mass treatment and vaccination of pigs
- Community education in health and pig husbandry
- Improved sanitation to end open defecation
- Improved meat inspection, control, and handling
- Better pig management.

The costs of implementing these approaches are not well defined.

Source: WHO 2009a.

sustainability and impact remain to be determined (Fiest and others 2014). A broad approach is needed to target stigma at the population level through legislation and advocacy. In addition, education and information provision to dispel myths and enhance seizure management among employers and teachers should empower those with epilepsy to seek treatment and encourage them to be more actively engaged in their communities. The cost-effectiveness of interventions to reduce stigma has not been formally assessed.

Legislation. One of the greatest contributors to the epilepsy treatment gap in LMICs is the lack of availability of anti-epileptic drugs. The second-generation medications are not available in the majority of countries, and even the older anti-epileptic drugs are only available sporadically. Investigators in Zambia who surveyed 111 pharmacies found that 49.1 percent did not carry anti-epileptic drugs. Pediatric syrups that are extensively used in HICs were universally unavailable (Chomba and others 2010). Regrettably, personal communications with epilepsy care providers in other LMICs suggested that this problem may be widespread (Chomba and others 2010).

Clearly, policies are warranted to guarantee the ongoing availability of affordable and efficacious anti-epileptic drugs to patients worldwide. Few countries have a separate budget for epilepsy services, and national funding support for epilepsy care is needed. Out-of-pocket expenses are the primary source of financing epilepsy care in 73 percent of low-income countries, including many countries in Africa, the Eastern Mediterranean, and South-East Asia, where the burden is highest (WHO 2011). Disability benefits do not exist in many regions, and patients are unable to receive monetary support.

Self-Management

Self-management is empowering patients to participate more actively in managing their care. Patients are likely to improve their understanding, adopt healthier lifestyles, and improve adherence to treatment (Fitzsimons and others 2012). Self-management can help those with epilepsy better identify and manage their seizure triggers, which can reduce frequency and decrease health services utilization and health care costs (Fitzsimons and others 2012). A few studies have examined the effectiveness of self-management education programs in adults and children and demonstrated some evidence of benefits; future research is needed to examine the cost-effectiveness of such programs in LMICs (Bradley and Lindsay 2008; Lindsay and Bradley 2010).

Pharmacological Interventions

The decision to initiate treatment with anti-epileptic drugs can be challenging. Analysis of the Multicentre trial for Early Epilepsy and Single Seizures suggests little benefit in initiating treatment for those who present with a single seizure, with no known neurological disorder, and normal electroencephalograms (EEGs) (Kim and others 2006). However, medical management should be considered in those who are at moderate to high risk, defined as more than two to three seizures at presentation, underlying neurological disorders, and abnormal EEGs (Kim and others 2006). More than 60 randomized control trials (RCTs), mostly in HICs, have examined the efficacy of anti-epileptic drugs, but there continues to be a lack of well-designed RCTs examining the efficacy of these medications for patients with generalized epilepsy syndromes and for children (Glauser and others 2013). Newer AEDs tend to be better tolerated, with fewer long-term side effects, but otherwise their superiority has not been proven.

Studies comparing the cost-effectiveness of anti-epileptic drugs in new onset epilepsy have not been conducted. A recent systematic review summarizes the evidence regarding their efficacy as initial monotherapy in those with epilepsy. Monotherapy with any of the standard anti-epileptic drugs (carbamazepine, phenobarbital, phenytoin, and valproic acid) should be offered to children and adults with convulsive epilepsy. Several lower-quality studies have demonstrated efficacy for phenobarbital in adults and children with partial onset seizures and generalized onset tonic-clonic seizures (Glauser and others 2013). Given the acquisition costs, phenobarbital should be offered as a first option if availability can be ensured. If available, carbamazepine should be offered to children and adults with partial onset seizures (WHO 2009b). Using the lowest possible dose should minimize side effects, improve seizure outcomes, and decrease the treatment gap. Valproic acid and ethosuximide have been shown to be most effective in the management of absence seizures, especially in children, although valproic acid is recommended, as it is on the list of essential medicines. Ethosuximide is available as a complementary medication. However, the medication should be avoided, when possible, in women of childbearing potential because of its higher association with major congenital malformations and poorer neurodevelopmental outcomes. Although newer therapeutic agents that are not metabolized by the liver are available, such as levetiracetam, the cost-effectiveness of such therapies has not been studied in LMICs.

Unfortunately, in LMICs, the availability and affordability of standard medications are poor and constitute barriers to treatment. One study found that the average

availability of generic medications in the public sector is less than 50 percent for all medicines, except diazepam injection. The private sector availability of generic oral medications ranged from 42 percent for phenytoin to 70 percent for phenobarbital. Public sector patient prices for generic carbamazepine and phenytoin were 5 and 18 times higher than international reference prices, respectively; private sector patient prices were 11 and 25 times higher, respectively. For both medicines, originator brand prices were about 30 times higher. The highest prices were observed in the lowest-income countries (Cameron and others 2012). Ensuring a consistent supply at affordable prices should be a priority.

Approximately 60 percent of patients in Sub-Saharan Africa do not have access to AEDs, increasing the risk of seizures, accidents related to seizures, and status epilepticus, a significant cause of morbidity and mortality in patients with epilepsy (Ba-Diop and others 2014). Some of the best patient-related strategies to avoid status epilepticus include adherence to treatment and avoidance of other seizure triggers. On a population level, the best way to avoid the morbidity and mortality associated with status epilepticus is through health policy to increase the availability of and access to AEDs, and through health professional education such that health professionals are aware that time is brain. Aggressive treatment of status epilepticus should be implemented after five minutes, not after 30 minutes of ongoing seizures, in accordance with the current operational definition of status epilepticus (Lowenstein and others 2001).

Management of Infectious Etiologies of Epilepsy

Neurocysticercosis is a common cause of epilepsy in LMICs. Recent evidence-based guidelines are available to guide the treatment of parenchymal neurocysticercosis (Baird and others 2013). These guidelines suggest that therapy with albendazole, with or without corticosteroids, along with AEDs, is likely to be effective in improving outcomes (Baird and others 2013).

Evidence-based guidelines were published to guide the selection of anti-epileptic drugs for people with HIV/AIDS, because concomitant AED-antiretroviral administration may be indicated in up to 55 percent of people (Birbeck and others 2012). The guidelines state that it may be important to avoid enzyme-inducing AEDs in people on antiretroviral regimens that include protease inhibitors or nonnucleoside reverse transcriptase inhibitors, because pharmacokinetic interactions may result in virologic failure. If such regimens are required for seizure control, patients may be monitored through pharmacokinetic assessments to ensure the efficacy of the antiretroviral regimen (Birbeck and others 2012).

Surgical Management

The probability of achieving one-year seizure freedom after trying up to three anti-epileptic drugs occurs in the majority of cases (70 percent in those presenting with new onset epilepsy). However, drug resistance occurs in up to 40% of patients overall, particularly in those with focal epilepsy (Berg and others 2009; Kwan and Brodie 2000; Schiller and Najjar 2008; Semah and others 1998). In those who have failed three anti-epileptic drugs, attempting to treat with additional anti-epileptic drugs is unlikely to achieve sustained seizure freedom (Jette, Reid, and Wiebe 2014). Experts generally agree that those who are drug resistant and have failed two appropriate AED trials should be considered for a surgical evaluation (Jette, Reid, and Wiebe 2014; Kwan and others 2010; Wiebe and Jette 2012). Other patients who should be referred to a comprehensive epilepsy program for a surgical evaluation include children with complex syndromes, patients with stereotyped or lateralized seizures or focal findings, and children with a magnetic resonance imaging lesion amenable to surgical resection regardless of seizure frequency (Jette, Reid, and Wiebe 2014; Wiebe and Jette 2012). Strategies for surgical therapy of epilepsies in resource-poor settings have been proposed, and epilepsy surgery is increasingly performed in LMICs, with excellent outcomes (Asadi-Pooya and Sperling 2008).

Alternative Therapies

Proposed alternative therapies for epilepsy include dietary therapies, medical marijuana, and acupuncture; only dietary therapies have been subjected to randomized trials. The ketogenic diet can improve seizure outcome in those with drug-resistant epilepsy, but is difficult to tolerate, particularly in adults (Levy, Cooper, and Giri 2012). The Atkins diet was associated with improved seizure control in one observational study, but future studies are required to examine its benefit and the benefit of other dietary therapies, such as the modified Atkins diet and the low glycemic index diet (Levy, Cooper, and Giri 2012). Despite their increased use, dietary therapies are resource intensive, costly, and remain largely limited to HICs (Cross 2013). Cost-effective and simpler means of implementing these therapies in LMICs are needed. The efficacy of oral cannabinoids and acupuncture for the treatment of epilepsy remains uncertain (Cheuk and Wong 2014; Koppel and others 2014).

Interventions to Optimize Health Care Delivery

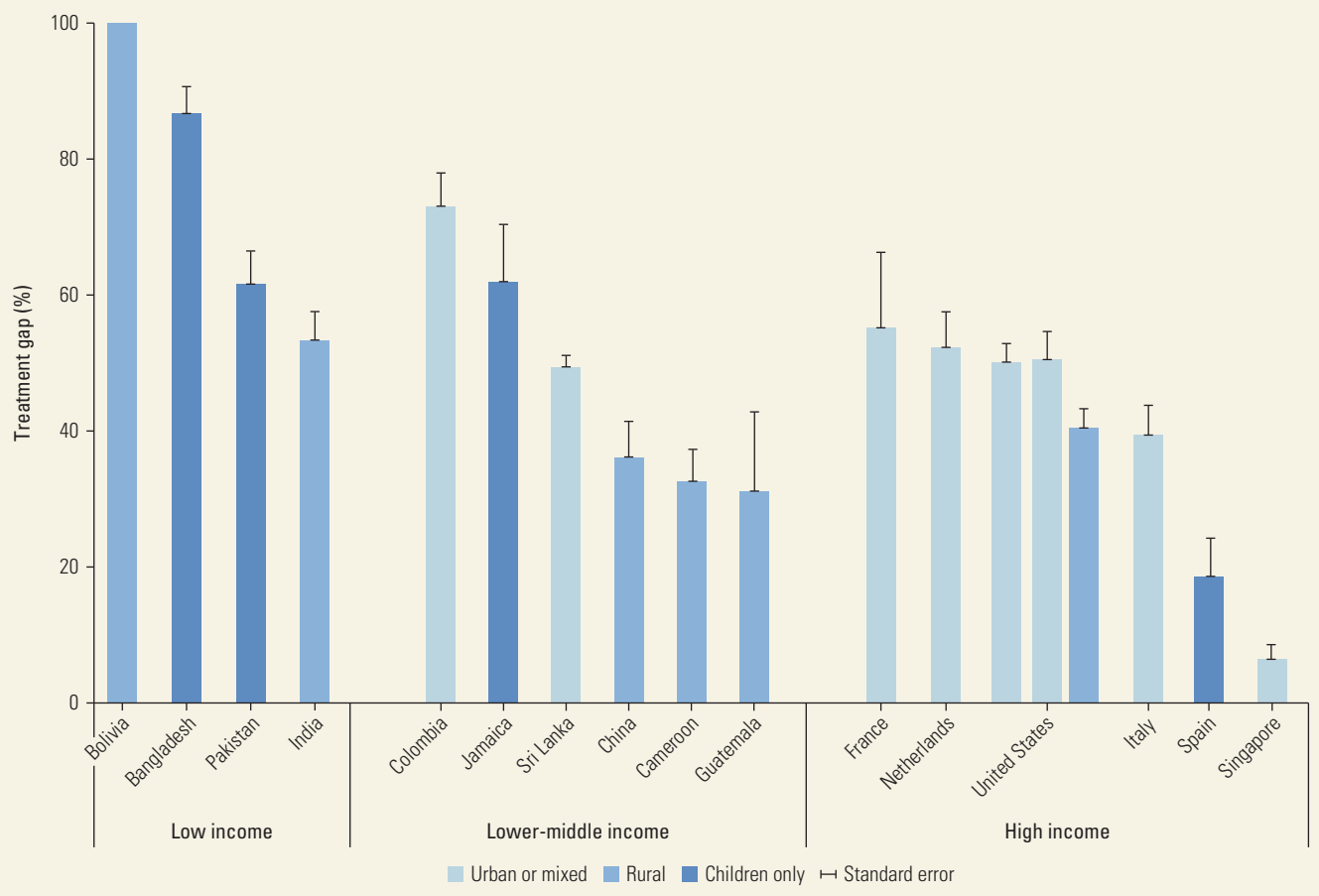
The treatment gap is defined as the number of people with active epilepsy who need appropriate anti-epileptic treatment but do not receive adequate medical therapy.

Regrettably, those living in LMICs, where the burden of epilepsy is extensive, are the most affected by the epilepsy treatment gap (Jette and Trevathan 2014). The treatment gap is more than 75 percent in low-income countries, more than 50 percent in many LMICs and upper-middle-income countries, and less than 10 percent in most HICs (figure 5.1) (Meyer and others 2010).

Proposed mechanisms for the epilepsy treatment gap can be divided into two broad categories: health care system and patient-related reasons (Cameron and others 2012; Kale 2002; Mbuba and others 2008). Health care system issues include lack of availability of anti-epileptic drugs, missed or delayed diagnosis, wrong treatment prescribed, treatment not offered to patients, and lack of resources and personnel (Cameron and others 2012; Kale 2002; Mbuba and others 2008). Epilepsy diagnosis is predominantly based on clinical history, and primary care physicians can be trained to provide basic treatment. Patient-related potential mechanisms for the treatment gap include cultural beliefs, stigma, fear of side effects, the hassle factor, and cost of treatment (Cameron and others 2012; Kale 2002; Mbuba and others 2008). All these reasons for the epilepsy treatment gap should be considered as potential targets for evaluation and action.

One study examined the availability, price, and affordability of anti-epileptic drugs in 46 countries (Cameron and others 2012). The study found that not only is the availability of these medications lower in LMICs, but their costs are highest where the treatment gap is the greatest (Cameron and others 2012). This study supports the view that availability and affordability of anti-epileptic drugs are likely major drivers in resource-poor countries. Box 5.3 provides a summary of the potential targets for evaluation and action to improve the epilepsy treatment gap.

Figure 5.1 Epilepsy Treatment Gap and Standard Errors Calculated from Lifetime Prevalence Estimates



Source: Meyer and others 2010.

Two of the most impactful approaches to target the treatment gap are legislative and anti-stigma interventions. Unfortunately, their cost-effectiveness has not been evaluated.

Cost-Effectiveness of Interventions

The cost-effectiveness literature is focused on the pharmacological management of seizures, meaning that economic evidence concerning interventions at the population and community levels, such as stigma reduction strategies, are minimal. A recent study in India showed that covering costs for both first- and second-line therapy and other medical costs alleviates the financial burden from epilepsy and is cost-effective across wealth quintiles and in all Indian states (Megiddo and others 2016). WHO conducted a cost-effectiveness analysis of epilepsy treatment in nine developing regions of the world (Chisholm and WHO-CHOICE 2005). Both studies found that first-line medications, such as phenobarbital, represent a highly cost-effective use of resources for health (see also chapter 12 in this volume [Levin and Chisholm 2015]).

Surgery has been shown to be cost-effective in appropriately selected candidates in HICs, with health care costs declining significantly after successful surgery (Jette, Reid, and Wiebe 2014, Langfitt and others 2007). A summary of health economic analyses of epilepsy surgery found that, in general, the costs per quality-adjusted life year for epilepsy surgery are well within the "very cost-effective" range recommended by the WHO (Jette and Wiebe 2015; Langfitt 1997). In the United States, for example, the incremental cost-effectiveness ratio was US$27,200, considering direct and indirect costs, which is well below the country's gross domestic product per capita of US$40,000. Unfortunately, economic evaluations of epilepsy surgery in children, older adults, and from LMICs are generally lacking. In addition, most economic analyses focus on temporal lobe surgery.

Conclusions

The dire consequences of poorly treated epilepsy include significant morbidity and mortality caused by seizures and related injuries. The ongoing stigma associated with seizures remains a major challenge to clinical care in many regions, as well as the poor access to proper medications that can adequately treat this population. Ultimately, it is likely that the most effective target to address the treatment gap of epilepsy globally will be legislative changes and anti-stigma interventions. Among the required legislative efforts are those that advocate better provision of benefits for functionally disabled persons with epilepsy, especially in resource-poor countries where they are most needed.

Box 5.3

Potential Targets to Improve the Epilepsy Treatment Gap

Health Care System

- Improve access to anti-epilectic drugs
- Improve training of health care professionals to decrease the proportion of misdiagnoses
- Improve training of health care professionals to ensure appropriate treatment
- Improve resources and consider cost-effective innovative health care delivery options.

Patient-Related Factors

- Improve knowledge about epilepsy to dispel myths and misconceptions about epilepsy, its causes, and its treatment
- Develop interventions to address stigma
- Implement policy and legislation to ensure access to and financial assistance for treatment.

DEMENTIA

Dementia poses a unique burden to those affected, their families, and societies. Substantial projected increases of patients with dementia in LMICs will pose additional economic and social burdens. Dementia is often erroneously considered an unavoidable part of aging or a condition for which nothing can be done; limited understanding and the persistence of stigma and discrimination limit help-seeking. Consequently, timely diagnosis is the exception rather than the norm; most people are not diagnosed and have limited access to adequate health or social care. Because pharmacotherapy and psychological and psychosocial interventions that can ameliorate symptoms and lessen the impact on family members and caregivers are often unavailable, the treatment gap remains very large, particularly in countries where cultural and infrastructure barriers persist.

Definitions

Dementia is a neuropsychiatric syndrome characterized by a combination of cognitive decline, progressive behavioral and psychological symptoms (BPSD), and functional disability (WHO 2012). Dementia is usually chronic and progressive; its insidious onset is typically characterized by objective deficits in one or more cognitive domains, such as memory, orientation, language,

and executive function that are at the late stages accompanied by behavioral disturbances. Although age is the most significant risk factor, dementia is not a normal part of aging (Ganguli and others 2000; Kukull and others 2002; Launer and others 1999). The clinical onset of dementia is marked by the impact of cognitive decline in everyday activities, and diagnosis is often made by physical and neurological examination with supporting evidence from informant interviews.

Dementia is a syndrome that includes Alzheimer's disease; vascular dementia; frontotemporal dementia; Lewy body dementia; and reversible causes, for example, hypercalcemia, thyroid hormone abnormalities, vitamin B12 and folic acid deficiencies, HIV, subdural hematoma, and normal pressure hydrocephalus. Alzheimer's disease accounts for 50–60 percent of all late-life dementias, and vascular dementia accounts for up to 15–20 percent. Although brain pathological lesions differ across dementia subtypes, mixed forms of dementia are common, and vascular brain damage often co-occurs.

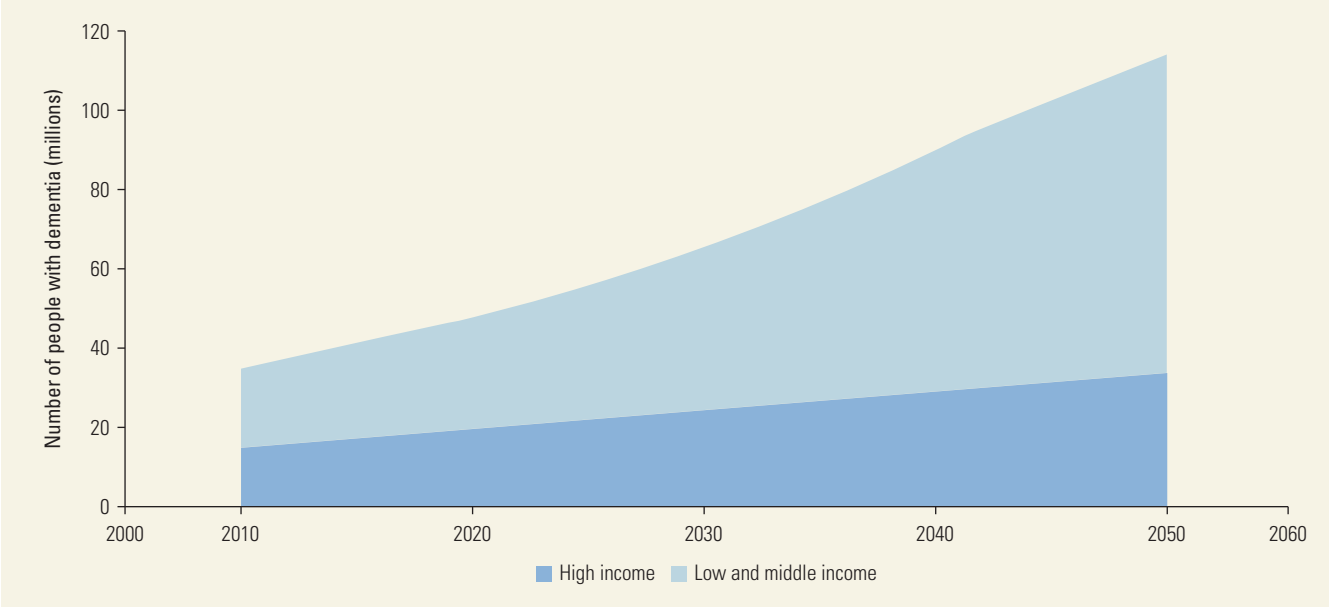
Epidemiology and Burden of Dementia

The most significant risk factor of dementia is increasing age; the incidence doubles with every five-year increment after age 65 (WHO 2015). The graying of societies in all global regions is expected to increase the number affected substantially. In 2015, approximately 47 million people had some form of dementia; 63 percent of those were in LMICs. This figure will nearly double to 76 million in 2030 and to 145 million by 2050. The majority (71 percent) of new cases will occur in LMICs (figure 5.2) (Prince and others 2015; WHO 2015). The steepest projected increases in numbers of people with dementia are expected in these settings because of rapid demographic changes. A new dementia case is diagnosed every four seconds in the world, leading to 7.7 million new cases per year; nearly 50 percent of new cases occur in Asia (WHO 2015).

In community-based samples, the prevalence of dementia varies from 38 to 400 per 100,000 inhabitants, with an increasing incidence over 55 years. Frontotemporal dementia (9.7 percent), alcohol-related dementia (9.4 percent), traumatic brain injury (3.8 percent), and Huntington's disease (3 percent) are more frequently present in early-onset dementia (EOD) compared with late-onset dementia (Picard and others 2011). Although dementia is more common in older age, some people develop symptoms at a younger age compatible with EOD, a poorly understood and frequently underdiagnosed condition.

Independent of the age at onset, most patients are cared for at home by close relatives. Need for one-on-one care starts early, becomes increasingly intense, and may change significantly throughout the natural history of the disease. Mood and behavioral changes, memory impairment for recent events, and spatiotemporal disorientation, as well as problem-solving deficits that characterize the early stage, may expose people with dementia

Figure 5.2 Projected Growth in Number of People with Dementia in All Income Groups, 2010–50



Source: WHO 2012.

and their families to stressful situations well before the clinical diagnosis is made. Later, mood and behavioral disorders further increase the burden of the disease.

The later stages are characterized by diffuse involvement with psychological and behavioral symptoms, including repetitive behaviors, hallucinations, aggression, and wandering (Kales and others 2014). In contrast to cognitive deficits, these symptoms are strongly related to institutionalization (Richardson and others 2013). Caring for persons with dementia is associated with increasing physical and emotional stress. Studies show that caregivers often have feelings of isolation, anxiety, and depression that reduce the quality of life and may impact the quality of care they provide (Reitz, Brayne, and Mayeux 2011). The cumulative distress of caregivers constitutes a central component of the dementia burden (Donaldson and Burns 1999).

Global Burden of Dementia

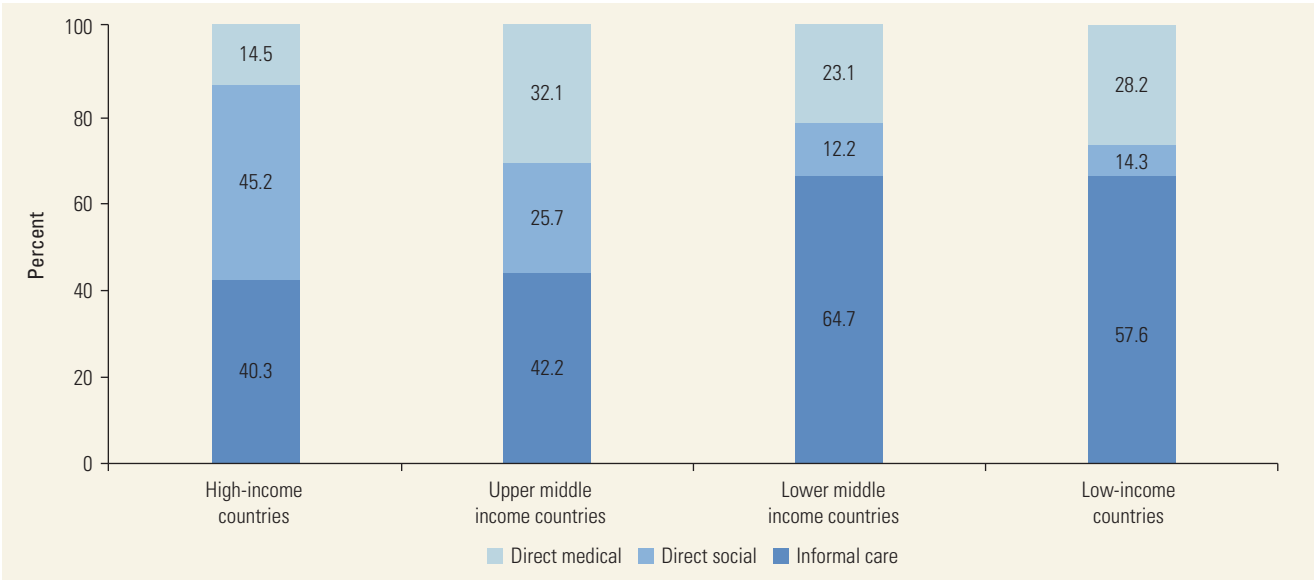
Dementia has become a significant economic burden across the world (figure 5.3). The disease is the leading cause of dependence in older adults in all world regions; up to 50 percent of older adults who need care have dementia. According to the 2010 GBD report, the DALYs attributable to Alzheimer's disease and other dementias doubled in the past 20 years, and dementia is estimated as the major driver of DALYs in late life among all chronic diseases by virtue of its strong association with mortality and dependence. The dementia-attributable DALYs may increase further in LMICs, where life expectancy is increasing, and resources for the provision of health care for older adults are limited or unavailable.

In HICs, the level of care needed is the single strongest predictor of institutionalization of older adults. In LMICs, institutionalization is less likely; people with dementia tend to stay in their homes through the very advanced stages of the disease, cared for by informal caregivers, who are almost invariably close relatives and women.

The direct costs include health service use, health care, and institutionalization; the indirect costs include those associated with cutting back on work to provide care. Both pose significant financial burdens on individuals, families, and societies.

The global economic cost in 2013 was US$604 billion, approximately 1 percent of the global gross domestic product (WHO 2015). The direct and indirect costs are proportionally higher in HICs. Moreover, the distribution of costs across medical, societal, and informal care varies strikingly across regions and health system organizations. Hospital inpatient costs contributed 70 percent of the direct costs for prevalent dementia, mainly related to psychiatric care (Leibson and others 2015). The indirect costs of informal care likely go far beyond foregone income. There are potentially pernicious repercussions on families and social ties, caused by caring for persons with dementia, particularly in settings where there are false beliefs about the causes and course.

Figure 5.3 Distribution of the Total Societal Costs of Dementia Care, by World Bank Income Level



Source: WHO 2012.

Interventions

Interventions need to address four key areas:

- Timely diagnosis
- Assessment and maintenance of physical health
- Cognition, activity, and well-being; assessment and treatment of BPSD
- Support for caregivers.

Detection and Diagnosis of Dementia

The evidence does not support dementia screening in the general population at present. Screening tools in primary health services may be used for those who report initial concerns about their cognitive function. Short versions of the Mini-Mental State Examination (Folstein, Folstein, and McHugh 1973) take as little as five minutes. However, unlike the Mini-Mental State Examination, which has been validated in several settings and languages, none of the short versions has been validated in LMICs, and their use is not recommended at present.

Diagnosis requires a clinical and informant interview and physical examination. Evidence from population-based studies, for example, the 10/66 culture-fair diagnostic algorithm (Prince and others 2003), suggests that diagnosis can be achieved using highly structured interviews and examinations conducted by trained community health workers. Adaptations for use in clinical practice are required, but the feasibility and cost-effectiveness of laboratory tests used in HICs to exclude treatable forms of dementia may limit their use in LMICs. Evidence from HICs indicates that the good practice of disclosure of the dementia diagnosis allows better planning and may limit distress; evidence from LMICs is lacking.

Appropriate adaptation to local culture, language, and beliefs should shape the design of programs and activities planned and implemented, and involve stakeholders, policy makers, the media, and local health care services. Health and social services should be enhanced to meet the projected increase in services.

Physical and Care Needs Assessment

Information on care arrangements and resources should be considered along with the evaluation of BPSD and the severity. A careful physical assessment is very important to monitor hearing and visual impairment, pain, constipation, urinary tract infections, and bedsores that may explain exacerbation of psychological symptoms. Whether physical assessment improves dementia prognosis, particularly the course of cognitive impairment, remains largely unknown. Nutritional status should be carefully monitored during the course of the disease. Weight loss is common and may start even before diagnosis. Loss of body weight may increase morbidity and mortality; yet, caregivers may be instructed on simple practices and techniques to overcome problems related to apathy and aversive feeding behaviors and may receive nutritional education to improve the caloric and nutritional content of meals. Finally, monitoring and effective treatment of vascular risk factors—including high blood pressure, hypercholesterolemia, smoking, obesity, and diabetes—should be encouraged to improve secondary prevention of cerebrovascular events. Moreover, there is extensive and persuasive evidence from mechanistic and well-designed prospective cohort studies that reducing the exposure to high blood pressure and hypertension in mid-life, and to diabetes in mid- and late life, as well as the reduction in tobacco use and increase in educational level of populations, can effectively reduce the dementia risk for populations (Prince and others 2014).

Pharmacological Interventions

Targets for pharmacological treatment include cognitive impairment; behavioral symptoms, such as agitation and aggression; and psychological symptoms, such as depression, anxiety, and psychosis. There is a large body of evidence for the efficacy of cholinesterase inhibitors (ChEIs), such as donepezil, rivastigmine, and galantamine, in the treatment of mild to moderate Alzheimer's disease (Institute for Quality and Efficiency in Healthcare 2014). The use of each of these medications is associated with modest and short-term comparable improvements in cognitive function, global clinical state, and activities of daily living. However, the evidence base for ChEIs in LMICs is limited. Moreover, the efficacy of this class of drugs in severe dementia is unclear, although behavioral symptom improvement was identified for galantamine (Institute for Quality and Efficiency in Healthcare 2014). A fourth drug for the treatment of cognitive impairment, memantine, has a different mode of action and is well tolerated, but evidence for its efficacy is limited to people with moderate to severe dementia. ChEIs and memantine are less efficacious in vascular dementia than other forms. Their efficacy in the treatment of behavioral disturbances is not established; manufacturer-sponsored licensing trials and post hoc analyses indicate small improvements.

Use of haloperidol and atypical antipsychotic medications for the treatment of agitation and behavioral symptoms with BPSD indicate small treatment effects, most evident for aggression, although these must be weighed against the associated mortality risk (Kales and others 2012). Atypical antipsychotic drugs have been widely prescribed for psychosis in dementia, but a meta-analysis of their efficacy indicated that only aripiprazole

and risperidone had a statistically and clinically significant effect on psychiatric symptoms (Tan and others 2015). An important caveat to the use of these medications in dementia is the associated increased risk of death and cerebrovascular adverse events. The literature of antipsychotic treatment in older people with dementia reveals that although improvement in behavioral disturbance was minimal after 6–12 weeks, there was a significant increase in absolute mortality risk of approximately 1 percent (Banerjee, Filippi, and Allen Hauser 2009). As the literature suggests that prescribing antipsychotics in dementia continues beyond 6–12 weeks, the harm of continued antipsychotic treatment in dementia is likely to be substantial. Therefore, many recommend nonpharmacological treatments, such as psychological and training interventions, to reduce BPSD rather than antipsychotic management (Deudon and others 2009).

A meta-analysis of the efficacy of antidepressants in people with dementia was inconclusive (Leong 2014). Antidepressants have been proposed for the treatment of BPSD with encouraging results (Henry, Williamson, and Tampi 2011).

Nonpharmacological Interventions

A well-conducted RCT of cognitive stimulation (reality orientation, games, and discussions based on information processing rather than knowledge) conducted in the United Kingdom as a group intervention, and a small pilot trial from Brazil, suggest that cognitive benefits from this intervention are similar to those for ChEIs (Aguirre and others 2013). More specific cognitive training produced no benefits. Cognitive rehabilitation, an individualized therapy designed to enhance residual cognitive skills and the ability to cope with deficits, showed promise in uncontrolled case series in HICs. A meta-analysis of four trials of reminiscence therapy (the discussion of past activities, events, and experiences) provides evidence for short-term improvement in cognition, mood, and caregiver strain, but the quality of these trials was poor (Bahar-Fuchs, Clare, and Woods 2013; Woods and others 2005; Woods and others 2012).

Interventions for Caregivers

A large literature attests to the benefits of caregiver interventions. These include psycho-educational interventions, often including caregiver training; psychological therapies, such as cognitive behavioral therapy and counseling; caregiver support; and respite care. Many interventions combine several of these elements. The outcomes studied include caregiver strain, depression, and subjective well-being; behavior disturbance and mood in the care recipient; and institutionalization.

Most caregiver-focused interventions reduce strain and depression, with cognitive behavioral therapy having the largest impact on depression (Aboulafia-Brakha and others 2014; Martín-Carrasco and others 2009; Selwood and others 2007; Van Mierlo and others 2012). Caregiver training models have been developed for dementia care, including the Maximizing Independence at Home project (Tanner and others 2015). Psycho-educational interventions required the active participation of the caregiver to be effective. Caregiver support increased well-being but no other outcomes.

For respite care, methodologically flawed RCTs showed no benefit on any outcome (Grant and others 2003; Maayan, Soares-Weiser, and Lee 2014). However, nonrandomized studies suggest that respite care significantly reduces caregiver strain and psychological morbidity (Ornstein and others 2014). Interventions targeting the caregiver may also have small but significant beneficial effects on the behavior of the person with dementia. A systematic review of 10 RCTs indicated a 40 percent reduction in the pooled odds of institutionalization; the effective interventions were structured, intensive, and multicomponent, offering a choice of services and supports (Tam-Tham and others 2013). Two small trials of a brief caregiver education and training intervention, one from India and one from Russia, indicated much larger treatment effects on caregiver psychological morbidity and strain than typically seen for such interventions in HICs (Gavrilova and others 2009; Dias and others 2008).

Interventions to Optimize Health Care Delivery

Interventions to Increase Demand for Services. Raising awareness among the public, caregivers, and health workers can lead to increased demands for services. Intergenerational solidarity can be promoted through awareness-raising among children and young adults. In many LMICs, many people with dementia live in multigenerational households with young children, who are the most frequent caregivers and the most likely to initiate help-seeking. The provision of disability pensions and caregiver benefits in LMICs is likely to increase requests for diagnostic assessment. Importantly, however, efforts to increase awareness must be accompanied by health system and service reforms, so that help-seeking is met with a supply of better prepared, more responsive services.

Interventions to Improve the Capacity of Health Care Teams. Primary health care services in LMICs often fail older people because the services are clinic-based, often

focused on simple curative interventions, and face high workloads. Given the frailty of many older people with dementia, there is a need for outreach to assess and manage patients in their own homes. Dementia care should be an essential component of any chronic disease care strategy. Training of nonspecialist health professionals should focus on case-finding and conveying the diagnosis to patients and caregivers together with information, needs assessment, and training and support. Training can be service-based, as well as through changes to medical and nursing schools, public health, and rural health curricula. Medical and community care services should be planned and coordinated to respond to the increasing need for support as the disease progresses.

Community-Based Programs to Deliver Effective Treatments. Programs to support caregivers can be delivered individually or in groups by community health workers or experienced caregivers. Strain, possibly associated with BPSD, should trigger more intensive interventions that include psychological assessment and depression treatment for the caregiver, respite care, and caregiver education and training. Such interventions could be incorporated into horizontally constructed, community-based programs that address the generic needs of frail, dependent, older people and their caregivers, whether these needs arise from cognitive, mental, or physical disorders. Recent evidence has demonstrated the effectiveness of delivery of Internet–based caregiver interventions (Czaja and Rubert 2002; Marziali and Garcia 2011).

Dementia: Cost-Effectiveness of Interventions

The estimated worldwide societal cost of dementia exceeded US$818 billion dollars in 2015 (Prince and others 2015). Direct costs include health service use and institutionalization; the indirect costs include those associated with inability to work and caregiver care. Both kinds of costs impose significant financial burdens on individuals, families, and societies. Informal care costs are proportionally highest in LMICs, while the direct costs for social care account for over half the costs in HICs (Prince and others 2015). Several studies, most in HICs, have evaluated the cost effectiveness of interventions in dementia. Particular challenges in such studies are the heterogeneity in etiology of dementia and the capture of cost-effectiveness in patients with milder forms of cognitive impairment.

Screening

A study in the Republic of Korea, where there is a nationwide early detection program for dementia, showed that the cost per quality-adjusted life year gained from early screening ranged from US$24,150 to US$35,661, depending on the age group. The probability of screening being cost-effective was highest in the group over age 75 years in a wide range of willingness to pay (WTP) (Yu and others 2015). The most cost-effective benefit of disease modifying therapies has been seen in moderate to severe dementia (Plosker and Lyseng-Williamson 2005).

Pharmacotherapy

Available pharmacoeconomic data from Europe and the United States support the use of memantine as a cost-effective treatment. Two cost-effectiveness analyses of memantine in moderate-to-severe Alzheimer's disease have been conducted in Finland and the United Kingdom; patient progression was simulated through health states related to dependency, residential setting, and cognitive function (Francois and others 2004; Jones and others 2004). Memantine reduced total societal costs by US$1,090 per patient per month, compared with no pharmacological treatment, over 28 weeks in a resource utilization and cost analysis conducted alongside a pivotal trial in patients in the United States with moderate-to-severe Alzheimer's disease (Wimo and others 2003). Results were primarily driven by reductions in total caregiver costs, which included the opportunity cost of time spent in caregiving tasks, and in direct nonmedical costs, which included the cost of care in a nursing home or similar institution.

An analysis in Canada found that treatment with rivastigmine yielded savings in the direct cost of caring for patients with Alzheimer's disease that exceed the cost of the drug after two years of treatment (Hauber and others 2000). In a 20-year Markov cohort model of disease modifying treatment in Alzheimer's disease based on a Swedish population, the sensitivity analysis implied no cost savings with disease modifying therapy, but most options indicated cost effectiveness verses the chosen WTP (Skoldunger and others 2013). In another study evaluating treatment with cholinesterase inhibitors or memantine for those with mild to moderate vascular dementia, donepezil 10 mg orally daily was found to be the most cost-effective treatment (Wong and others 2009).

Other Therapies

In terms of nonpharmacologic therapies, cognitive stimulation therapy has been shown to be cost-effective for people with mild-to moderate dementia when delivered biweekly over 7 weeks though was found to have modest effects when continued for longer when added to administration of acetylcholinesterase inhibitors (D'Amico and others 2015). An exercise intervention was found to have

the potential to be cost-effective when considering behavioral and psychological symptoms but did not appear cost-effective when considering quality-adjusted life year gains. The START (STrAtegies for RelaTives) study, a randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of a manual-based coping strategy program in promoting the mental health of carers of people with dementia, found the intervention to be cost-effective with respect to caregiver and patient outcomes, and National Institute for Health and Care Excellence (NICE) thresholds (Livingston and other 2014). In a health economic analysis of resource costs and costs of formal care on a psychosocial intervention for family caregivers of persons with dementia, those in the intervention group reported higher quality of life while their spouse was living at home (Dahlrup and others 2014).

Conclusions

Research for early diagnosis is important in view of the future availability of treatments that are likely to be more efficacious in the early stages of the disease, when diagnosis is more difficult. At present, there are no disease-modifying pharmacological treatments for dementia, and medications to treat symptoms appear to have limited efficacy (Birks 2006; McShane, Areosa Sastre, and Minakaran 2006). The ambitious goal to identify a cure for Alzheimer's disease by 2025, which was announced by world political leaders in 2013 during the G8 meeting in London, underscores the recognition of dementia as a global health threat and priority. However, the quest for a cure should not drain resources from research on modifiable risk factors, which remains crucial for prevention, to potentially delay the symptomatic onset or slow the disease progression. The first WHO Ministerial Conference on Global Action Against Dementia was held in March 2015 to foster awareness of the public health and economic challenges posed by dementia and improve the understanding of the roles and responsibilities of Member States and stakeholders; it led to a Call for Action supported by conference participants. Indeed, a broad public health approach to address the complex challenges of dementia is extremely important.

HEADACHE DISORDERS

The three headache disorders of particular public health importance are migraine, TTH, and MOH. Collectively, these three are the third most common cause of disability in populations throughout the world (Murray and others 2012; Steiner and others 2015; Stovner and others 2007; Vos and others 2012).

Headache disorders are the most frequent cause of consultation in primary care and neurology practice; it prompts many visits to internists; ear, nose, and throat specialists; ophthalmologists; dentists; psychologists; and proponents of a wide variety of complementary and alternative medical practices (WHO 2011). Headache is a common presenting symptom in emergency departments. The consequences of recurring migraine include pain, disability, diminished productivity, financial losses, and impaired quality of life. Therefore, although headache rarely signals serious underlying illness, its causal association with personal burdens of pain, disability, and diminished quality of life makes it a major contributor to ill health.

Definitions

Migraine

Migraine is a disorder commonly beginning in puberty and often lasting throughout life. Episodic attacks have a frequency of once or twice a month on average, but this may vary widely, subject to lifestyle and environmental factors. In women, prevalence is higher because of a hormonally-driven association with menstruation. Headache, nausea, and photophobia are the most characteristic attack features. In some attacks, about 10 percent overall, and in only one-third of people with migraine, headache is preceded by aura symptoms, most commonly visual. The headache itself, lasting for hours to two to three days, is typically moderate or severe and unilateral, pulsating, and aggravated by routine physical activity (International Headache Society 2013). Chronic migraine, with headache attacks on 15 or more days per month and/or loss of episodicity, is a particularly disabling form (Natoli and others 2010).

Tension-Type Headache

TTH is a highly variable disorder, commonly beginning in the teenage years and reaching peak levels for people in their 30s. It lacks the specific features and associated symptoms of migraine, with headache usually mild or moderate, generalized, and described as pressure or tightness (International Headache Society 2013).

Medication-Overuse Headache

MOH is earning recognition as a disorder of major public health importance for three reasons: it is an attribute of migraine or (less often) TTH; it is highly disabling at individual levels; and it is iatrogenic and avoidable. MOH affects between 1 and 2 percent of the general population (Westergaard and others 2014), up to 67 percent of the chronic headache population, and 30–50 percent of patients seen in specialized headache centers (Evers, Jensen, and European Federation of

Neurological Societies 2011). The cause is chronic excessive use of medications taken initially to treat episodic headache (Diener and Limmroth 2004). The overuse of all such medications is associated with this problem, although the mechanism through which it develops undoubtedly varies among drug classes (Steiner and others 2007).

Epidemiology and Burden of Disease

Estimating the global burden of headache disorders is a challenging task, given data paucity for many LMICs, variations in methodologies in epidemiological studies, and variation of cultural attitudes related to the reporting of complaints. Much of the world's population lives in countries where headache prevalence and burden are incompletely known (Stovner and others 2007). Regardless, estimations have been done and show that the global one-year prevalence of migraine constitutes 14.7 percent and TTH 20.8 percent of adults ages 18–65 (Murray and others 2012). The prevalence of all types of headache occurring on 15 or more days per month (including chronic migraine, chronic TTH, and MOH) is 3 percent (Stovner and others 2007). Although the prevalence of migraine is markedly lower in Asia (Stovner and others 2007) and was thought to be so in Africa, a study in Zambia has indicated a high one-year prevalence (22.9 percent), coupled with very high prevalences of headache on 15 or more days a month (11.5 percent) and probable MOH (7.1 percent), with considerable economic impact (Mbewe and others 2015).

Interventions

Worldwide, at least 50 percent of headaches are self-treated, even in high-income countries (HICs) (WHO 2011). Professional health care, when needed, should be provided in primary care settings for the majority of cases (WHO 2011), and guidelines for the management of headache disorders in these settings are available (Steiner and others 2007). History and examination should take due note of warning features that might suggest an underlying condition (Steiner and others 2007).

Many instruments, including the HALT questionnaire, are available to assess the burden of headache symptoms on individual patients. (Steiner and Martelletti 2007). Realistic goals of management include understanding that primary headaches cannot be cured but can be managed effectively. We focus our further treatment discussions on migraine.

Self-Management

Stress is a common predisposing factor for migraine. Improving the ability to cope is an alternative treatment approach, but the role of psychological therapies in migraine management is unclear. Most research has focused on high-end intensive treatment of individual cases of disabling and refractory headache, which has limited relevance to public health. Yet there is potential for low-cost delivery of group behavioral training, and even some very limited evidence of benefit (Mérelle and others 2008). This approach could be further explored in LMICs.

Obesity is a risk factor for migraine, especially for frequent migraine (Evans and others 2012). Regular exercise and keeping fit can be beneficial. A study among obese adolescents with migraine found a significant improvement in headache in those who participated in a 12-month weight-loss program (Evans and others 2012).

Pharmacological Interventions

Guidelines recommend a stepped-care approach commencing with acute treatment using simple analgesics (aspirin or one of several other nonsteroidal anti-inflammatory drugs) (Steiner and others 2007). Good evidence demonstrates the efficacy and tolerability of aspirin (Kirthi, Derry and Moore 2013), ibuprofen (Rabbie, Derry and Moore 2013), and diclofenac potassium (Derry, Rabbie, and Moore 2013). The most desirable outcome of acute treatment is complete relief from pain within two hours, without recurrence or need for further medication and without adverse events. This outcome is not commonly experienced with simple analgesics alone.

The more easily achievable outcome referred to as *sustained headache relief* (SHR) is defined as reduction of pain to no worse than mild within two hours of treatment, also without recurrence or need for further medication. Mild pain is assumed not to be associated with disability, and SHR implies full functional recovery when functional impairment was present initially. Aspirin alone provides SHR in an estimated 39 percent of users (Kirthi, Derry and Moore 2013); this is a modest effect in the sense that it leaves 61 percent without this benefit but at the same time is among the most cost-efficient interventions to improve public health (Linde, Steiner, and Chisholm 2015). Aspirin has the advantages of being universally available and on the WHO essential medicines list (WHO 2013). Ibuprofen provides SHR in a somewhat higher estimated proportion of users (45 percent) (Rabbie, Derry, and Moore 2013), at variable but not always higher cost. Diclofenac is considerably more costly, without significantly greater efficacy

(Derry, Rabbie, and Moore 2013). It is argued that the anti-inflammatory effect is important in acute migraine treatment, and paracetamol is therefore rather less effective than aspirin (at the same cost) or other nonsteroidal anti-inflammatory drugs (Derry and Moore 2013; Steiner and others 2007).

Antiemetics should also be used in acute treatment, and should not be restricted to patients who are vomiting or likely to vomit. Nausea is one of the most aversive and disabling symptoms of a migraine attack and should be treated appropriately (Silberstein and others 2012). Gastric stasis is a feature of migraine; prokinetic antiemetics, such as domperidone or metoclopramide, enhance gastric emptying and promote the efficacy of oral analgesics in migraine.

The usual second step in management is still acute treatment, with the substitution or addition of specific anti-migraine therapy (Steiner and others 2007). Ergotamine tartrate remains in use in many countries (WHO 2011), but it is poorly bioavailable, is not highly effective, and has potential side effects. Of the triptan class of agents–which are specific anti-migraine medications–seven are available in many countries. They differ somewhat in their pharmacokinetics, and they are not identical in efficacy; however, the differences between them are small when set against the up to tenfold price differences between sumatriptan (available in generic versions) and the other six. Sumatriptan is available in four formulations (oral, intranasal, rectal, and subcutaneous). Sumatriptan 50 mg orally provides SHR in an estimated 35 percent of users (Derry, Derry, and Moore 2012), much the same as aspirin; however, it has a different mode of action, and responses to each drug are independent. When sumatriptan is used on its own, its cost-effectiveness is at least two orders of magnitude lower than that of aspirin (Linde, Steiner, and Chisholm 2015); it is usually reserved as a second-line treatment for those who fail to respond to first-line treatments (Steiner and others 2007). In adults and children, regular use of acute medications at high frequency (more than two days per week) risks the development of MOH.

Prophylactic medications are used in step three to reduce the number of attacks occurring when acute therapy is inadequate (Steiner and others 2007). There is adequate or good evidence of efficacy and tolerability for propranolol (Linde and others 2013b), amitriptyline (Dodick and others 2009), valproate (as sodium valproate or valproic acid) (Linde and others 2013b), and topiramate (Diener and others 2004; Linde and others 2013a). To assess outcome as migraine attacks averted requires comparison with an untreated base line, which is available for propranolol (28 percent) (Linde, Steiner, and Chisholm 2015), amitriptyline (44 percent) (Linde, Steiner, and Chisholm 2015). In an American Academy of Neurology review, divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, and timolol were found to be effective for migraine prevention (Silberstein and others 2012). In terms of cost, propranolol and amitriptyline are similar and very low, and topiramate is much higher; amitriptyline might be the choice of prophylactic drug when resource conservation is the key consideration (Linde, Steiner, and Chisholm 2015). However, the mode of action of these medications in migraine is unknown, and failure of response to one does not predict the failure of others (Steiner and others 2007), which might be tried when amitriptyline is ineffective and resources permit.

Alternative Therapies

Acupuncture and physical therapies, such as spinal manipulation, requiring direct one-to-one therapist-patient interaction, are highly resource intensive, and have questionable efficacy (Bronfort and others 2004; Linde and others 2009) to justify their recommendation. Even the limited benefits seen in clinical trials may not be replicated in the real world, where therapists operate under time constraints.

Public Education Programs

Public education programs can help to improve migraine outcomes. Lifestyle factors may predispose people to or aggravate migraine. Although the evidence is poor that modifying lifestyle is an effective way of controlling migraine, avoidance of trigger factors is a logical stratagem (Steiner and others 2007).

Public education about the increasing risk of migraine with obesity (Bronfort and others 2004) may achieve some benefits, because, unlike many other ill-health consequences of obesity, headache is experienced in the present. Public education also appears to offer the most effective means of controlling a potential epidemic of MOH as a consequence of mistreated migraine. Recent evidence from the Global Campaign against Headache (Mbewe and others 2015) suggests this may be a particular problem in LMICs where medications are relatively more affordable and available than health care. The initial effectiveness of simple analgesics encourages their further use, which is not problematic at low frequency. With increasing frequency comes greater reliance and increasing risk of MOH. Once MOH is established, medication overuse is likely to escalate.

The incremental health benefits obtained in LMICs from adding educational programs to the use of over-the-counter and prescription medications appear to be achievable at acceptable incremental costs (Linde, Steiner, and Chisholm 2015). Pharmacists can be a key

source of information to the public about headache disorders, treatments, and the dangers of medication overuse, but only if this role is explicitly recognized in their reimbursement, and only if their advice is sought. Further, the cost-effectiveness of treatments may increase with public education programs to improve adherence to treatments (Linde, Steiner, and Chisholm 2015).

Interventions to Optimize Health Care Delivery

In a global survey, one-third of responding countries recommended improved organization and delivery of health care for headache so that care would be efficient and equitable (WHO 2011). The organization of services to achieve this goal is clearly a challenge, and no single solution may be appropriate in all settings. Most patients do not require specialist expertise or special investigations (Steiner and others 2007), and the three-tier service model developed by the Global Campaign against Headache for Europe (Steiner and others 2011) is highly adaptable. This model had been used as part of demonstration projects to structure headache services in China (Yu and others 2014), and in Sverdlovsk Oblast in the Russian Federation (Lebedeva and others 2013). Using the model, about 90 percent of patients are managed in first-level care, usually but not necessarily by physicians; 1 percent require specialist care that is necessarily hospital-based. The intermediate 9 percent do not require specialist care, but may have diagnostic or management difficulties that would benefit from second-level care. Provision of this level of care depends on resources and local health service organizations. Each level must maintain a gatekeeper role to higher levels to make the model work.

Countries that have invested in headache services have, paradoxically, generally done so by setting up specialist headache clinics. Worldwide, the proportion of headache patients seen by specialists is 10 percent (WHO 2011), indicating considerable scope for resource reallocation for the benefit of more patients if the levels below were better utilized. Pharmacists need to be formally integrated into health care systems.

Training Health Care Providers. The ability of first-level services to deliver effective care depends on the providers—physicians, clinical officers, or nurses—having the basic knowledge required. Evidence clearly indicates deficiencies, and better professional education ranked far above all other proposals for change in WHO's global survey (WHO 2011). Training first-level doctors in the management of migraine is likely to improve outcomes, as well as to increase the cost-effectiveness of prescription medications (Linde, Steiner, and Chisholm 2015). Furthermore, such training might reduce waste, through reductions in the high rates of unnecessary investigations to support diagnosis (WHO 2011).

Cost-Effectiveness of Interventions

There is a lack of nationally conducted cost-effectiveness studies to inform resource allocation decisions for headache disorders in LMICs. However, a recent cost-effectiveness modeling analysis of migraine treatment was carried out for four countries–China (an upper-middle-income country), India (a lower-middle-income country), Russia (an HIC), and Zambia (a lower-middle-income country). The analysis concluded that acute treatment with aspirin generated a year of healthy life for less than US$100 (Linde, Steiner, and Chisholm 2015), making it among the most efficient interventions to improve population health. Cost-effectiveness analysis was not carried out for paracetamol specifically, because the only evidence of SHR came from 42 highly atypical patients in the United States (Linde, Steiner, and Chisholm 2015). When sumatriptan is used on its own for acute management of migraine, its cost-effectiveness is at least two orders of magnitude less favorable than that of aspirin, which indicates why sumatriptan is reserved as a second-line treatment for those who fail to respond to first-line treatments (Steiner and others 2007).

Prophylactic medications are less cost-effective than acute therapy with simple analgesics, but considerably more cost-effective than acute therapy with the combination of analgesics and triptans (when needed), but this may be true only if prophylactics are reserved for those with three or more attacks per month (Linde, Steiner, and Chisholm 2015). The addition of educational programs (posters and leaflets in pharmacies) for the use of over-the-counter and prescription medications appears to increase population health gain at an acceptable incremental cost, as does training providers (Linde, Steiner, and Chisholm 2015).

Conclusions

It is clear that investment in structured headache services, with their basis in primary care and supported by educational initiatives aimed at professionals and the public, is the way forward for most countries. Such services require resource reallocation which is easily justified economically. Importantly, services for migraine would simultaneously provide for the other common and disabling headache disorders. The gains

in population health achievable through effective headache management are substantial and independent of any recovery of indirect costs attributable to these disorders. The financial costs to society through lost productivity from migraine alone are enormous: more than €100 billion (US$100 billion) per year in the European Union (Linde and others 2012) and far higher than the health care expenditure on headache in any country (WHO 2011). Greater investment to treat migraine effectively through well-organized health services supported by education may well be cost-saving overall (WHO 2011).

CONCLUSIONS AND RECOMMENDATIONS

Epilepsy, dementia, and headache disorders represent a significant burden on global health. Not only are these conditions prevalent, but they are associated with significant disability, poor psychosocial outcomes, and substantial economic costs.

Innovative health care management approaches are required in LMICs because of the lack of specialist care. Some of these approaches are discussed, but few have been subjected to cost-effectiveness evaluations. Further data collection is needed in many areas of global neurology, including epidemiological studies, needs assessments, and cost-effectiveness analyses.

For all three of these conditions, pharmacotherapies have advanced considerably in the past two decades, but these options are regrettably limited in LMICs. Indeed, the treatment gap for these conditions is substantial, driven by patient and health system factors, which are unlikely to improve without education of the public and health care professionals, legislation, and anti-stigma interventions. Fortunately, attitudes and knowledge about the burden of epilepsy, dementia, and migraine are starting to improve, and such progress can help reduce the treatment gap and enhance psychosocial outcomes for those suffering from these conditions. Ultimately, however, increased financial investments and legislative changes are required to improve neurological care in LMICs.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  a) lower-middle-income = US$1,046 to US$4,125
  b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

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