CHAPTER __. Neurological Disorders

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Abstract

Emerging trends in the disease burden worldwide show that neurological diseases are of critical importance and that the burden of neurological disorders will grow exponentially in low and middle-income settings over the next decade. Patients with neurological disorders often require significant socioeconomic support due to physical, cognitive and psychosocial limitations. Despite the high prevalence of disability, there is increasing recognition that neurological services and resources are disproportionately scarce, especially in low-income countries. This chapter reviews the epidemiology of three major neurological disorders—migraine, epilepsy, and dementia—with a discussion of the treatment gaps and evidence on effective interventions, both population-wide and community-level, as well as a cost-effective analysis to alleviate the burden of disease.

Keywords: Neurological disorders, migraine, headache, epilepsy, seizure, dementia

Introduction

Neurological disorders, conditions involving pathology of the brain, spine, or peripheral nervous system, pose a large burden on worldwide health. The Global Burden of Disease (GBD) study has drawn attention to the burden of worldwide disability associated with neurological disorders (Murray and others 2012). The most recent estimates show that the neurological disorders included in the GBD—Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, migraine and tension-type headache—represent 3 percent of the worldwide burden of disease (Murray and others 2012). Although a seemingly small overall percentage, the four brain disorders of dementia, epilepsy, migraine, and stroke rank in the top 50 causes of disability-adjusted life years (DALYs) (Murray and others 2012).

This chapter uses the World Health Organization (WHO) regions: Africa, the Americas, South-East Asia, Europe, Eastern Mediterranean, and Western Pacific.

Migraine and epilepsy represent a staggering one-third and a one-fourth of this neurological burden, respectively (Murray and others 2012). Although dementia and Parkinson's disease rank slightly lower overall, they are two of the top 15 conditions with the most substantial increase in burden in the past decade. In the 2010 GBD report, 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).

In the next decade, the neurological burden of disease is expected to exponentially grow in low- and middle-income countries (LMICS) as aging populations increase (WHO 2006).

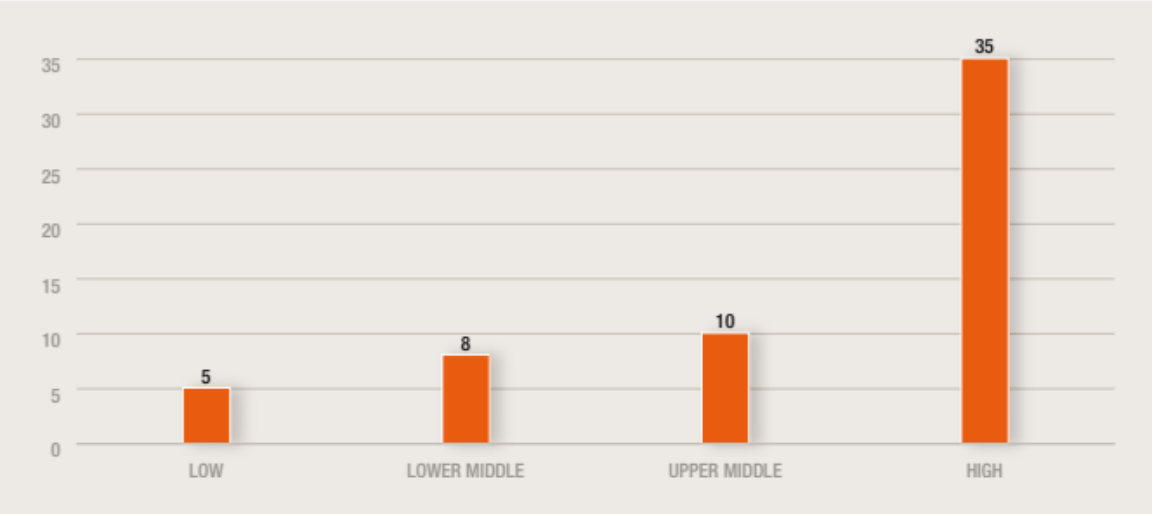
Despite the significant impact of neurological disorders on patients and societies, knowledge of their epidemiology, including variation in disease frequency across place and time and understanding of associated risk factors and outcomes, remains limited, particularly in LMICs. Patients with neurological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

This chapter addresses the epidemiology and management of three neurological disorders: migraine, epilepsy, and dementia (Murray and others 2012). 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.

Migraine

Headache occurs as a characteristic symptom of a large number of primary and secondary headache disorders (Olesen and others 2013). Migraine is the most frequent cause of consultation in both primary care and neurological practice; it prompts many visits to internists; ear, nose, and throat (ENT) specialists; ophthalmologists; dentists; psychologists; and proponents of a wide variety of complementary and alternative medical practices WHO 2011). Migraine 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; each of these is important in its own right. Therefore, while headache rarely signals serious underlying illness, its causal association with these personal burdens of pain, disability, and damaged quality of life makes it a major contributor to ill health.

Figure __.1 Countries with Information on the Societal Impact of Headache, by World Bank Income Category



Source: WHO 2011.

Note: % positive responses among those responding.

The three headache disorders of particular public health importance are migraine, tension-type headache (TTH), and medication-overuse headache (MOH). Collectively, these three are the cause of disability in populations throughout the world (Stovner and others 2007; Vos and others 2012; WHO 2011).

Definitions

Migraine

Migraine is a recurrent 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. Headache, nausea, and photophobia are the most characteristic attack features. In some attacks, about 10 percent overall, and only in one-third of people with migraine, headache is preceded by aura symptoms of reversible cortical dysfunction, 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 (Olesen and others 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 in the 30s. It lacks the specific features and associated symptoms of migraine, with

headache usually mild or moderate, generalized, and described as pressure or tightness. There are distinct subtypes. Episodic TTH occurs, like migraine, in attack-like episodes, which usually last for a few hours but can persist for several days. Chronic TTH occurs 15 or more days every month and can be unremitting over long periods (Olesen and others 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; it is highly disabling at individual levels; it is iatrogenic and avoidable. The cause is chronic excessive use of medications taken initially to treat episodic headache (Diener and Limmroth 2004). All such medications, in overuse, are associated with this problem, although the mechanism through which it develops undoubtedly varies among drug classes. Over time, headache episodes become more frequent, as does medication intake. MOH is oppressive and persistent, and, if not stopped, eventually unremitting, fluctuating with medication use repeated every few hours.

Epidemiology and Burden of Disease

Estimating the global burden of headache disorders is a challenging task, given the significant data paucity for many LMICs, varying methodologies in epidemiological studies, and variation of cultural attitudes related to the reporting of complaints. Few epidemiological studies exist in Eastern Europe, Australia/Oceania and Africa; much of the world's population live in countries where headache prevalence and burden are incompletely known (Stovner and others 2007). Despite these challenges, efforts have been made to estimate the global burden of headache.

Burden of migraine

In a systematic review on the global prevalence of headache disorders, the prevalence of headache was 47 percent, current migraine 10 percent, current TTH 38 percent, and current chronic daily headache 3 percent (Stover and others 2007). The prevalence of headache in general was found to be approximately 50 percent in Asia, Australia, and Europe and North America, but markedly lower in Africa at 20 percent (Stovner and others 2007). It is reported that 50 percent to 75 percent of the adults ages 18–65 years have had headache in the past year (Stovner and others 2007). It is clear that headache disorders are a worldwide problem, affecting individuals of all ages, races, income levels, and geographical areas.

Interventions

Worldwide, at least 50 percent of headaches are self-treated, even in HICs (WHO 2011). Professional health care, when needed, should be provided in primary settings for the majority of cases (WHO 201), 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). It is important to assess and acknowledge the impact that headache has on the lives of patients, family members, and work colleagues. The HALT questionnaire is an instrument to assess the burden of headache symptoms on individual patients (table x.3) (Steiner and Martelletti 2007).

Table __. Headache-Attributed Lost Time (HALT) Index

HALT Index (Headache-Attributed Lost Time)

Q1. On how many days in the last three months could you no go to work or school because of your headaches?

Q2. On how many days in the last three months could you do less than half your usual amount in your job or schoolwork because of your headaches? (Do not include days you counted in question 1 where you missed work or school)

Q3. On how many days in the last three months could you not do any household work because of your headaches?

Q4. On how many days in the last three months could you do less than half your usual amount of household work because of your headaches?

Grading (I-IV)

0-5	Minimal or infrequent impact	Grade I
6-10	Mild or infrequent impact	Grade II
11-20	Moderate impact	Grade III
20+	Severe impact	Grade IV

Source: Steiner and Martelletti 2007.

Realistic goals of management include understanding that primary headaches cannot be cured but can be managed effectively. We focus our discussions on migraine headaches.

Drug Treatments for Migraine

Guidelines recommend a stepped-care approach commencing with acute treatment using simple analgesics (aspirin or one of several other nonsteroidal anti-inflammatory drugs or paracetamol (Steiner and others 2013). Good evidence demonstrates the efficacy and tolerability of aspirin (Kirthi and others 2013), ibuprofen (Derry and Moore 2013), paracetamol (Derry and Moore 2013), and diclofenac potassium (Derry 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 achieved 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 to not be associated with disability, and SHR implies full functional recovery if there functional impairment occurred initially. Aspirin alone provides SHR in an estimated 39 percent of users (Kirthi and others 2013); this is a modest effect in the sense that it leaves 61 percent without this benefit. However, in a cost-effectiveness analysis applied to (China (UMIC), India (LMIC), the Russian Federation (HIC), and Zambia (LMIC), this treatment generated a whole year of healthy life for less than US$100 (Derry and others 2013), putting it among the most efficient interventions to improve population health. Aspirin has the advantages of being universally available and on the World Health Organization's (WHO) essential medicines list for migraine (World Health Organization 2013). Ibuprofen provides SHR in a somewhat higher estimated proportion of users (45 percent) (Rabbie and others 2013), at variable but not always higher cost. Diclofenac is considerably more costly, without significantly greater efficacy (Derry and others 2013). Cost-effectiveness analysis was not possible for paracetamol because the only evidence of SHR came from 42 highly atypical patients in the United States (Derry and Moore 2013). It is argued that anti-inflammatory effect is important in acute migraine treatment, and paracetamol is rather less effective than aspirin (at the same cost) or other NSAIDs (Derry and Moore 2013; Westergaard and others 2014).

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 acute treatment, with the substitution or addition of specific antimigraine therapy (Westergaard and others 2014). Ergotamine tartrate remains in use in many countries (WHO 2011), but it is poorly bioavailable, not highly effective, toxic, and subject to accumulation. Of the triptan class of drugs—which are specific antimigraine drugs—seven are available in many settings. 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 10-fold 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 (Linde and others 2015), 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 (Derry and others 2013); it is usually reserved as second-line treatment for those who fail to respond to first-line treatments (Westergaard and others 2014). Sumatriptan may be used in the higher oral dose of 100 mg when circumstances warrant, or in any of the other formulations; efficacy may be higher and cost will be considerably so. Subcutaneous sumatriptan is reserved for situations where rapid response is of overriding importance. Important contraindications for ergotamine and triptans include pregnancy, as well as patients with cardiac disease or risk factors for it.

In adults and children, regular use of acute medication at high frequency (more than two days per week) risks the development of MOH. Prophylactic drugs are used in step three to reduce the number of attacks occurring when acute therapy is inadequate (Westergaard and others 2014).

There is adequate or good evidence of efficacy and tolerability for propranolol (Linde and others 2015), amitriptyline (Derry and others 2012), valproate (as sodium valproate or valproic acid), (Linde and others 2003) and topiramate (Dodick and others 2009). To assess outcome as migraine attacks averted requires comparison with an untreated base line, which is available for propranolol (28 percent) (Linde and others 2013), amitriptyline (44 percent) (Derry and others 2012), and topiramate (40 percent) (Dodick and others 2009). In terms of cost, propranolol and amitriptyline are similar and very low, and topiramate much higher; amitriptyline might be the choice of prophylactic drug when resource-conservation is the key consideration. However, the mode of action of these drugs in migraine is unknown, and failure of response to one does not predict failure of others; others might be tried when amitriptyline is ineffective and resources permit.

Prophylactic drugs 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. However, this may be true only if prophylactics are reserved for those with three or more attacks per month, a clinically reasonable threshold.

Other Treatments

Self-management and alternative therapies

Stress is the most 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 has most obvious application in **LMICs** and warrants exploration.

Acupuncture and physical therapies, such as spinal manipulation, requiring direct one-to-one therapist-patient interaction, are highly resource-intensive, and have questionable efficacy (Linde and others 2009; Bronfort and others 2004) 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.

Regular exercise and keeping fit are always beneficial. Obesity is a risk factor for migraine, especially for frequent migraine (Evans and others 2012). One study of 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). It is not known how widely this finding can be extrapolated.

Public Education Programs

Cost-effectiveness of treatments may increase with public education programs to improve adherence to treatments (Rabbie and others 2013), although there were untested assumptions built into the model that led to this conclusion. Public education programs can help to improve migraine outcomes in other ways. Lifestyle factors may predispose 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 (Westergaard and others 2014). Missing meals and missing sleep are often identified, but the real trigger may be whatever caused these.

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 appears also 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 (unpublished) suggests this may be a particular problem in **LMICs** where drugs are affordable and available but health care is not. 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. 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 drugs appear to be achievable at acceptable incremental costs (Rabbie and others 2013). Pharmacists can be a key source of information to the public about headache disorders, the 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.

Interventions to optimize health care delivery and target the treatment gap

In the WHO's global survey (WHO 2011), one third of responding countries recommended improved organization and delivery of health care for headache.

Headache services need be delivered countrywide efficiently and equitably (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 2011). The three-tier service model developed by the Global Campaign against Headache for Europe (Steiner and others 2011) is highly adaptable. Headache

services in China have been structured in accordance with this model (Yu and others 2014), and it underlies a demonstrational initiative in Sverdlovsk Oblast in Russia (Yu and others 2014); discussion is underway in Zambia. Using the model, about 90 percent of patients are managed in first-level care, usually by physicians, but not necessarily; 1 percent requires specialist care, which is not necessarily hospital-based. The intermediate 9 percent does not require specialist care but may have diagnostic or management difficulties that would benefit from second-level care. Where or whether this level of care is provided depends on resources and local health service organizations. To make the model work, each level must maintain a gatekeeper role to higher levels.

No cost-effectiveness studies have been conducted to compare these levels, but first-level services are provided at the lowest cost. 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 utilized. Pharmacists need to be formally integrated into health care systems.

Professional Education

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 indicated deficiencies, and better professional education ranked far above all other proposals for change (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 (Rabbie and others 2013). 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 low- and middle-income countries. However, a recent cost-effectiveness modelling analysis of migraine treatment was carried out for three middle-income countries (Russia, India, China) and one low-income (Zambia) (Linde and others 2015). The authors compared first- and second-line acute drug treatment as well as prophylactic treatment. Acute treatment with aspirin generated a year of healthy life for less than US$100 (Derry and others 2013), putting 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 US patients (Derry and Moore 2013), from which it was unwise to extrapolate to other countries. 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 (Derry and others 2013), which indicates why it is reserved as second-line for those who fail to respond to first-line treatments (Westergaard and others 2014). Prophylactic

drugs 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 (a clinically reasonable threshold). The addition of educational programmes (posters and leaflets in pharmacies) to use over-the-counter and prescription drugs appear to increase population health gain at an acceptable incremental cost, as does training of providers (Linde and others 2015).

Conclusions

Migraine is increasingly recognized as a chronic debilitating disorder, and more work is needed to disseminate this information and reduce related morbidity. Few health ministries prioritize headache disorders. National strategies to commission cost-effective services are required to meet the needs of affected people, but the lack of epidemiological data, especially in **LMICs** presents significant difficulties. Health ministries cannot prioritize activities that would achieve optimal outcomes or measure their cost-effectiveness without knowing the true prevalence and impact of 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: over 100 billion Euros (over 100 billion US dollars) per year in the European Union (Lebedeva and others 2013), 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).

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). However in 2014, the International League Against Epilepsy provided an enhanced definition of epilepsy (box 1) (Fisher and others 2014).

Box 1 – A person has epilepsy if they meet any of the following criteria:

(1) At least two unprovoked (or reflex) seizures occurring >24 h apart

(2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

(3) A diagnosis of an epilepsy syndrome

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 they remained seizure free for the past 10 years and were off antiseizure medications for at least the past five years (Fisher and others 2014).

Epilepsy can be broadly classified into three categories: structural or metabolic epilepsies (for example, epilepsy due to a remote stroke), epilepsies of genetic or presumed genetic origin (for example, juvenile myoclonic epilepsy), and epilepsies of unknown causes (Berg and others 2010). Example 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 2010). Perinatal and infection-related etiologies often predominate in LMICs.

Epidemiology and Burden of Disease

Prevalence, Incidence, and Mortality

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 and others 2009; Benamer and Grosset 2009; Burneo and others 2005; Forsgren and others 2005; Mac and others 2007). The median incidence per 100,000 per year is higher in LMICs at 81.7 (IQR 28.0-239.5) compared to HICS at 45.0 (IQR 30.3-66.7) (Ngugi and others 2011). Higher estimates of prevalence or incidence rates reported in many LMICs are thought to be due to 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 (Banerjee and others 2009). In HICs, where 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 and others 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 due to status epilepticus (Ngugi and others 2014). Other common causes of premature mortality in epilepsy include acute symptomatic disorders (for example, brain tumor or stroke), sudden unexpected death in epilepsy (SUDEP), suicides, and accidents (Hitiris and others 2007).

Epilepsy ranks as the 36th leading cause of DALYs according to the Global Burden of Disease 2010 report, although ranks as high as the 14th leading cause of DALYS in Western Sub-Saharan Africa. Epilepsy ranks higher globally in terms of YLDs, 20th overall, second only to migraine in terms of brain disorders (Vos and others 2012). Importantly, models in the GBD 2010 report to calculate the global burden of epilepsy considered only the previously termed idiopathic/cryptogenic epilepsy and not epilepsy secondary to causes such as infections, stroke, or genetic syndromes. 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, Uganda, and Tanzania 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 to reducing symptomatic epilepsies (particularly due to 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 due to neurocysticercosis was reduced from 36.9 percent in 1997 to 13.9 percent in 2005, although the overall incidence and prevalence did not differ between time periods (Medina and others 2011). The overall cost of this study was US$1.33 million, although an economic analysis was 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 due to taenia solium was not examined, but the findings represent a positive step. The expert consultation report on foodborne infections, such as taeniasis/cystercosis, proposes some approaches to ensure sustainable prevention and control of

Box 2 – Approaches to ensure sustainable prevention and control of neurocysticercosis

(1) Preventive chemotherapy of human taeniasis through mass or targeted treatment of humans
(2) Mass treatment and vaccination of pigs
(3) Community education in health and pig husbandry
(4) Improved sanitation to end open defecation
(5) Improved meat inspection, control and handling and
(6) Better pig management although costs of implementing these approaches are not well defined

this often endemic agent- these approaches are listed in Box 2 (World Health Organization 2011). The report did not define the costs of implementing these approaches (WHO 2011).

Anti-Stigma Interventions

People with epilepsy and their families must bear the weight imposed on them as a result of stigmatization (Fiest and others 2014). 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 access to education are frequent. Many children are taken out of school when diagnosed. 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 sustainability of these changes and the impact on long-term outcomes 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.

Personal Interventions

Self-management and self-care. 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).

Medical management with antiseizure medications. The decision to initiate treatment with antiseizure medications can be challenging. Analysis of the Multicentre trial for Early Epilepsy and Single Seizures (MESS) suggests little benefit in initiating treatment to those who present with a single seizure, no neurological disorders, and normal EEGs (Kim and others 2006). However, medical management should be considered in those who are at moderate to high risk (more than two to three seizures at presentation, neurological disorders, and abnormal EEGs) (Kim and others 2006). Although more than 60 randomized controlled trials (RCTs) have examined the efficacy of antiseizure medications (mostly in HICs), there continues to be a lack of well-designed RCTs examining the efficacy of antiseizure medications for patients with generalized epilepsy syndromes and for children (Glauser and others 2013). Studies comparing the cost-effectiveness of antiseizure medications in new-onset epilepsy have not been conducted. No trial has shown the superiority of the new antiseizure medicines over older agents, although some newer medications tend to be better tolerated and have been associated with fewer long-

term side effects. A recent systematic review summarizes the evidence regarding the efficacy and effectiveness of antiseizure medications as initial monotherapy in those with epilepsy (Glauser and others 2013).

Monotherapy with any of the standard antiepileptic drugs (carbamazepine, phenobarbital, phenytoin, and valproic acid) should be offered to children and adults with convulsive epilepsy. Although no level evidence is available for phenobarbital, a number of lower quality studies have demonstrated its efficacy 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 2009). 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. On the other hand, it should be avoided (when possible) in women of childbearing potential due to its higher association with major congenital malformations and poorer neurodevelopmental outcomes.

Unfortunately, in LMICs, the availability and affordability of standard medications are poor and constitute barriers to treatment. A recent study found that the average availability of generic medications in the public sector is less than 50 percent for all medicines, except diazepam injection (Cameron and others 2012). The private sector availability of generic oral medications ranged from 42.2 percent for phenytoin to 69.6 percent for phenobarbital. Public sector patient

prices for generic carbamazepine and phenytoin were 4.95 and 17.50 times higher than international reference prices, respectively; private sector patient prices were 11.27 and 24.77 times higher, respectively. For both medicines, originator brand prices were about 30 times higher. The highest prices were observed in the lowest income countries (Cameron and others 2012). Ensuring a consistent supply at affordable prices should be a priority.

Management of Infectious Etiologies of Epilepsy

Neurocysticercosis (NCC) is a common cause of epilepsy in LMICs. Recent evidence-based guidelines are available to guide the treatment of parenchymal NCC (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 selection of antiseizure medicines 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 ARV regimen (Birbeck and others 2012).

Surgical management. Although the probability of achieving one-year seizure freedom after trying up to three antiseizure medications occurs in the majority of cases (70 percent in those presenting with new onset epilepsy), some cases of drug resistance have been reported, 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 antiseizure medications, attempting to treat with additional antiseizure medications is unlikely to achieve sustained seizure freedom (Jette and others 2014). There is Experts generally agree that those who are drug resistant should be considered for a surgical evaluation (Jette and others 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 an MRI lesion amenable to surgical resection regardless of seizure frequency (Jette and others 2014; Wiebe and Jette 2012). Strategies for surgical therapy of epilepsies in resource-poor setting have been proposed, and epilepsy surgery is increasingly performed in LMICs with excellent outcomes (Asadi-Pooya and Sperling 2008). Surgery has been shown to be cost-effective in appropriately selected candidates in HICs, and health care costs declining significantly after successful surgery (Jette and others 2014).

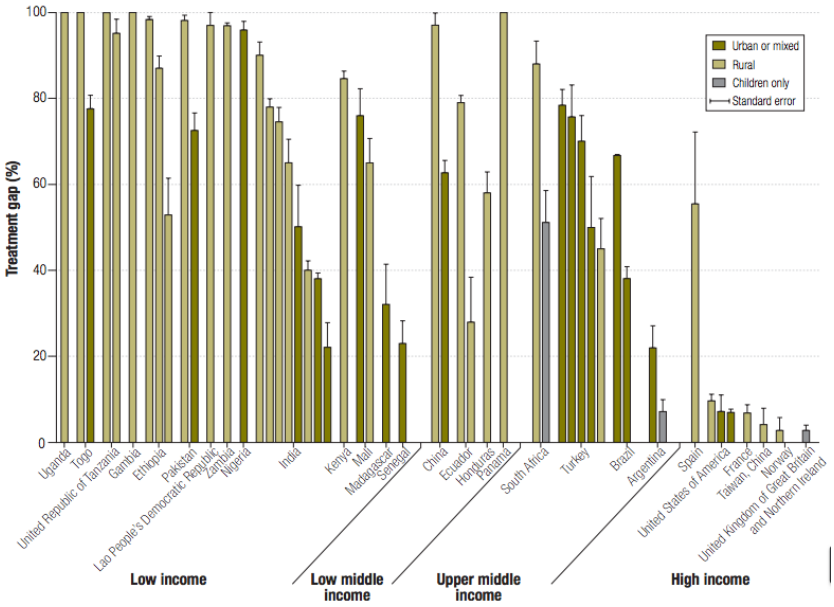
Alternative therapy. Proposed alternative therapies for epilepsy include dietary therapies, medical marijuana, and acupuncture; only dietary therapies have been subjected to randomized trials. The ketogenic diet can improve seizure outcome in those with drug-resistant epilepsy but is difficult to tolerate, particularly in adults (Levy and others 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 and others 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 and target the treatment gap

The treatment gap is defined as the number of people with active epilepsy who need appropriate antiepileptic treatment but do not receive adequate medical therapy. Regrettably, those living in low and middle income countries where the burden of epilepsy is extensive, are most affected by the epilepsy treatment gap (Jette and Trevathan 2014). The treatment gap is more than 75% in low income countries, more than 50% in many lower middle and upper middle income countries and less than 10% in most high income countries (Figure 1) (Meyer and others 2010).

Figure __.2 Epilepsy Treatment Gap (percent) and Standard Errors, by Country and World Bank Income Category



Source: 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 (Kale 2002; Mbuba and others 2008; Cameron and others 2012). Health care system causes include unavailability of antiseizure medications, missed or delayed diagnosis, wrong treatment prescribed, treatment not offered to patient and lack of resources (e.g. trained personnel) (Kale 2002; Mbuba and others 2008; Cameron and others 2012). It is important to note that epilepsy diagnosis is predominantly based on clinical history and primary care physicians can be trained to adequately train and provide basic treatment of epilepsy. Patient related potential mechanisms for the treatment gap include cultural beliefs, not seeking treatment (i.e. due to felt stigma), fear of side effects, hassle factor and cost of treatment (Kale 2002; Mbuba and others 2008; Cameron and others 2012). All of these reasons for the epilepsy treatment gap should be considered as potential targets for evaluation and action. A recent study indeed examined the availability, price and affordability of antiseizure medications in 46 countries (Cameron and others 2012). The authors found that not only is the availability of antiseizure medications poorer in low and middle income countries but costs for these medications were also highest in these countries, where the treatment gap is the greatest (Cameron and others 2012). This study confirms that availability and affordability of antiseizure medicines are likely major drivers in resource poor countries. A summary of the potential targets for evaluation and action to improve the epilepsy treatment gap are listed in Box 2.

However, two of the most impactful approaches to target the treatment gap are legislative and anti-stigma interventions. These are discussed below. Unfortunately, the cost-effectiveness of either has not been evaluated.

Box 2 – Potential targets for evaluation and action to improve epilepsy treatment gap

Health care system
Improve access to antiseizure medications
Improve training of health care professionals to decrease proportion of misdiagnoses
Improve training of health care professionals to ensure "right" treatment prescribing
Improve resources (e.g. personnel) 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
Interventions to address stigma
Policy and legislation to ensure access to and financial assistance for treatment

Legislation

One of the greatest contributors to the epilepsy treatment gap in LMICs is the unavailability of antiseizure medications. The second-generation medications are not available in the majority of countries, and even the older antiseizure medications are only available sporadically.

Investigators in Zambia who surveyed 111 pharmacies found that 49.1 percent did not carry antiseizure medications. Pediatric syrups that are extensively used in HICs were universally unavailable (Chomba 2010). Regrettably, personal communications with epilepsy care providers in **other LMICs** suggested that this problem may be widespread (Chomba 2010). Clearly, policies are warranted to guarantee the ongoing availability of affordable and efficacious antiseizure medications 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 **LICs**, including many regions of Africa, South-East Asia, and the Eastern Mediterranean, where the burden is highest (WHO 2011). Disability benefits do not exist in many regions, and patients are unable to receive monetary support.

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-level, such as stigma reduction strategies have yet to be formally assessed. Even studies comparing the cost-effectiveness of commonly used anti-seizure medications against one another in new onset epilepsy have also not been carried out. Surgery has been shown to be cost-effective in appropriately selected candidates in high income countries with health care costs declining significantly after successful surgery (Jette and others 2014). WHO also conducted a cost-effectiveness analysis of epilepsy treatment in nine developing regions of the world (Chisholm, 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 of this Volume). Most recently, Megidoo et al (2015) conducted an extended cost-effectiveness analysis of these intervention strategies in the context of India. This analysis likewise concluded that treatment with first-line medication is the most cost-effective and least costly strategy to implement from a public payer perspective but also showed that increased service and financial coverage of first- and second-line AEDs as well as surgery for those in need would generate the greatest overall level of health gain and offer the greatest level of financial protection at the population level.

Conclusion

The dire consequences of poorly treated epilepsy include significant morbidity and mortality due to the 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 impactful target to address the treatment gap of epilepsy globally will be legislative changes and anti-stigma interventions. Among required legislative efforts will be those that advocate for better provision of benefits for functionally disabled persons with epilepsy, especially in resource-poor countries where they are most needed.

Dementia

Dementia poses a unique burden to those affected, their families, and societies. Most dementia patients live in LMICs, and substantial projected increases 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 its 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 progressive behavioral and psychological symptoms (BPSD) and functional difficulties (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, reasoning, and behavior. 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 on everyday activities, and diagnosis is often made by physical and neurological examinations and clinical and 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 to 60 percent of all late-life dementias, and vascular dementia accounts for up to 15 to 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

Dementia affects an estimated 44.35 million individuals worldwide. The most prominent risk factor is increasing age; the incidence doubles with every five-year increment after age 65 (WHO 2012). There are no significant geographical variations in prevalence or incidence, and the graying of societies in all regions is expected to substantially increase the number affected. Recent estimates suggest that prevalent cases will double every 20 years, reaching 135.5 million by 2050 (figure __.3) (Prince 2013).

Figure__.3 Projected Growth in Numbers of People with Dementia in All Income Groups 2010-2050

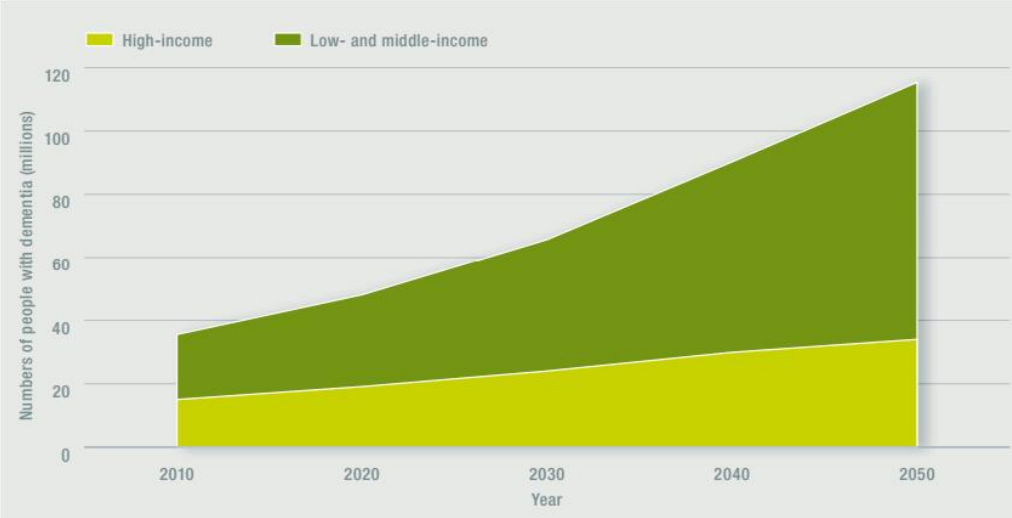


FIG 2.3 Growth in numbers of people with dementia in high-income and low- and middle-income countries

Source: WHO 2012.

The large majority of people with dementia live in LMICs, and the steepest projected increases in numbers are expected in these settings due to rapid demographic changes. A new dementia case is diagnosed every four seconds in the world, approximately 7.7 million new cases per year, nearly 50 percent of which occurs in Asia. Dementia is an epidemic in all income groups.

Most patients are cared for at home by close relatives, and the need of care (also referred to as *dependence*) has some important characteristics that stem from dementia out of many other chronic conditions. Need for one-on-one care starts early, becomes increasingly intense, and may qualitatively change significantly throughout the natural history of the disease. Mood and behavioral changes, along with memory impairments for recent events and spatiotemporal confusion that characterize the early stage of the disease, may expose people with dementia and their families to stressful situations well before the clinical diagnosis is made. Dementia is burdensome because its clinical onset and symptoms inexorably worsen and change. The later stages are characterized by diffuse involvement with psychological and behavioral symptoms, including repetitive behaviors, hallucinations, aggression, and wandering (Kales and others 2014). Caring for persons with dementia is associated with increasing physical and emotional burdens. Studies show that caregivers often have feelings of isolation, anxiety, and depression that reduce their quality of life and may impact the quality of care they provide (Mayeux and others). The cumulative distress of caregivers (Donaldson and others 1999) constitutes a central component of the dementia burden.

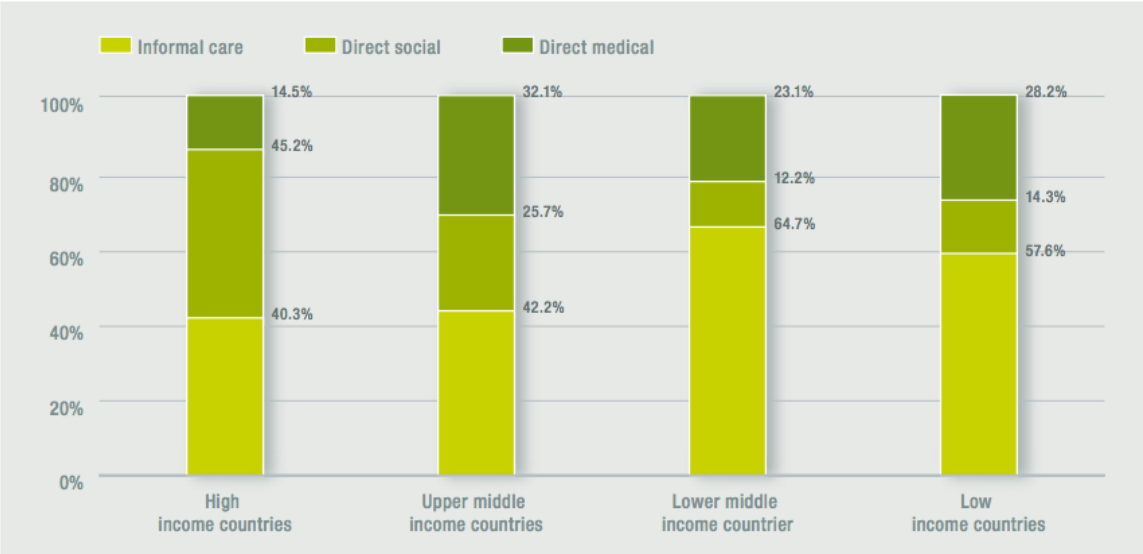
Global burden of dementia

Dementia is the leading cause of dependence in older adults in all world regions; up to 50 percent of older adults who need care has 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 institutionalizations 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.

Dementia has become a significant economic burden across the world (figure __.4).

Figure __.4 Distribution of Total Societal Costs of Dementia Care, by World Bank Income Level



Source: WHO 2012.

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 (GDP). Both the direct and indirect costs are proportionally higher in HICs. Moreover, the distribution of costs across medical, **societal** and informal care vary markedly across regions and health system organizations. However, the indirect costs of informal care go likely far beyond foregone income. There are potentially pernicious repercussions on families and social ties due to caring for persons with dementia, particularly in settings where persist false beliefs about the causes, course, and consequences of the disease, with additional risks of psychological distress for caregivers.

Interventions

Interventions should address four key areas: timely diagnosis; assessment and maintenance of physical health, cognition, activity, and wellbeing; assessment and treatment of BPSD; and caregivers' support.

Detection and Diagnosis of Dementia

Help seeking by those who have significant perceived problems due to the clinical onset of dementia symptoms is limited in both HICs and LMICs. Increased awareness and understanding are needed. 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 of services. 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 and Folstein 1974) take as little as five minutes. However, unlike the MMSE, 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 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. An important component of the needed future improvement in detection and diagnosis in LMICs is how the diagnosis should be communicated to patients and families. 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.

Physical and Care Needs Assessment

Information on care arrangements and resources should be considered along with the evaluation of the BPSD and the severity. A careful physical assessment is very important to monitor hearing and visual impairments, 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. During the course of the disease, nutritional status should be carefully monitored. Weight loss is common and may start very soon after diagnosis. Loss of body weight may increase the risk of comorbidity and mortality; 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 calorie and nutritional content of meals. The cost-effectiveness of supplements to improve nutritional status in LMICs has not been tested, but resources constraints may limit their use. 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. However, improved vascular care does not seem to improve the course of dementia.

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 strong 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 comparable improvements in cognitive function, global clinical state, and activities of daily living. The evidence base for ChEIs in LMICs is limited. The efficacy of this class of drugs in severe dementia is unclear, although psychopathological 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 for the treatment of disturbed behavior is not established; manufacturer-sponsored licensing trials and post hoc analyses indicate small improvements.

Use of haloperidol and atypical antipsychotic drugs for the treatment of agitation and behavioral and psychological symptoms with BPSD indicate small treatment effects, most evident for aggression, although these must be weighed against the associated mortality risk. Atypical antipsychotic drugs have been widely prescribed for psychosis in dementia, but a meta-analysis of their efficacy indicated that only aripiprazole had a statistically and clinically significant effect. An important caveat to the use of these medications in dementia is the associated increased risk of death and cerebrovascular adverse events. Two studies that reported mortality (Ballard and others 2008; Devanand and others 2012) showed no significant difference between the continuation of antipsychotics and discontinuation groups, although in the long-term follow-up of the Ballard The DART-AD Trial, there was a statistically nonsignificant increase in mortality in people on prolonged antipsychotic therapy. The literature of antipsychotic treatment in older people with dementia reveals that although improvement in behavioral disturbance was minimal after 6 to 12 weeks, there was a significant increase in absolute mortality risk of approximately 1 percent (Banerjee and others 2009). As the literature suggests that prescribing of antipsychotics in dementia continues beyond 6 to 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. Antidepressants have been proposed for the treatment of BPSD, but a meta-analysis of trazodone was inconclusive. Citalopram showed efficacy over placebo for the treatment of agitation in one small RCT, while sertraline showed no benefit on any primary behavioral endpoint.

A systematic review of trials of anticonvulsants to treat BPSD found sodium valproate to be ineffective. Carbamazepine may be more promising, with large benefits noted for global clinical outcomes and agitation in one small parallel group trial and more marginal effects in a small pilot trial (Prince 2009).

Nonpharmacological Interventions

A well-conducted RCT of cognitive stimulation (reality orientation, games, discussions based on information processing rather than knowledge) conducted in the United Kingdom as a group intervention, and a small pilot trial from Brazil, suggests 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 (Woods and others 2005).

Interventions for Caregivers

A large literature attests to the benefits of caregiver interventions. These include psychoeducational interventions, often including caregiver training; psychological therapies, such as cognitive behavioral therapy (CBT) and counseling; caregiver support; and respite care. Many interventions combine several of these elements. Outcomes studied include caregiver strain, depression, and subjective wellbeing; behavior disturbance and mood in the care recipient; and institutionalization.

Most caregiver-focused interventions seemed to reduce strain and depression, with CBT having the largest impact on depression (Aboulafia-Brakha and others 2014; Martín-Carrasco and others 2009). Psychoeducational interventions required the active participation of the caregiver to be effective. Caregiver support increased wellbeing but no other outcomes.

For respite care, three methodologically flawed RCTs showed no benefit on any outcome (Grant and others 2003; Korn and others 2012; Maayan and others 2014). However, nonrandomized studies suggest that respite care significantly reduces caregiver strain and psychological morbidity (Stern 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 in LMICs of a brief carer education and training intervention, one from India and one from the Russian Federation, indicated much larger treatment effects on caregiver psychological morbidity and strain than typically seen for such

interventions in HICs (Gavrilova and others 2009; Prince 2009; Saldanha and others 2010).

Health Service and Care Organization

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 are 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 they are clinic-based, preoccupied with 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 on conveying the diagnosis to patients and caregivers together with information and support, needs assessment, and training and support. Training can be service-based, as well as through changes to the 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. Caregiver-support programs can be delivered individually or in groups by community health workers or experienced caregivers. Strain, whether 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 carer interventions (Czaja and others 2002; Marziali and others 2006; Powell and others 2008).

Conclusion

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 and others 2006; McShane and others 2006). The ambitious goal to identify a cure for Alzheimer's disease by 2025 announced by world political leaders in 2013 during the G8 in London certainly testifies to 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. Indeed, a broad public health approach to address the complex dementia challenges is extremely important.

Conclusions and Recommendations for Neurological Disorders

Migraine, epilepsy and dementia represent a significant proportion of the burden of neurological disease. Not only are these conditions prevalent, but they also are associated with significant disability, poor psychosocial outcomes and substantial economic costs.

For all three of these conditions, drug therapies have advanced considerably in the past two decades but regrettably medical therapies are limited in low and middle income countries. Indeed, the treatment gap for these conditions can be substantial in many developing countries. This treatment gap is driven by a number of patient and health system related factors, which are unlikely to improve without ongoing education (of the public and of health care professionals), legislation (e.g. better access to drug therapies) and anti-stigma interventions.

Innovative health care management approaches are also required in low and middle income countries due the lack of specialist care. Some of these approaches are discussed but few if any have been subjected to cost effectiveness evaluations.

Fortunately, attitudes and knowledge about each of these conditions is improving, and such progress can help reduce the treatment gap and enhance psychosocial outcomes for those with migraine, epilepsy and dementia. Ultimately however, increased financial investments and legislative changes are required to improve neurological care in low and middle income countries.

Note

<<unnumbered>>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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