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Introduction

Diseases of the central nervous system (CNS) are of an enormous diversity. They can range from diseases that are present from an early stage of life to those that are primarily of a later-age onset. For a long time, CNS disease was labelled and stigmatised by society, with it being believed that the sufferers were possessed by demons or evil spirits, or that it was the consequence of some personality deficit or weakness in the afflicted individual. In the nineteenth and early twentieth century, the prevailing attitudes resulted in the committing of many mentally ill individuals to asylums. Such attitudes were hard to shift, and residues of them are still apparent. The alterations in attitudes to mental health and its treatment can most vividly be seen with the remarkable reduction in the population suffering from mental illness in long-term residential care (Figure 1.1), and consequential growth in the treatment of patients within their communities (Manderscheid *et al.*, 2009). The process of deinstitutionalization and psychiatric reform gathered momentum after World War II, originally in the United States and UK, but gradually spread across the world (Novella, 2008). The consequences were that, in the United States, there was a peak in the number of residents in the mid 1950s. This peak coincides with the introduction of the first pharmacological treatments for psychosis and depression. Since then, after nearly 50 years of decline, the resident population in psychiatric institutions is beginning to stabilise at around 50,000, with a modest rise even being seen in 2005, which may be due to a number of factors, including demographic age-related and ethnic changes, as well as pressures on the provision of community services (Manderscheid *et al.*, 2009).

The major challenge in the pharmacological treatment of disorders of the brain is that they have a greater complexity than most other diseases or conditions. For example, most other diseases have a well-defined biological origin, from which drug

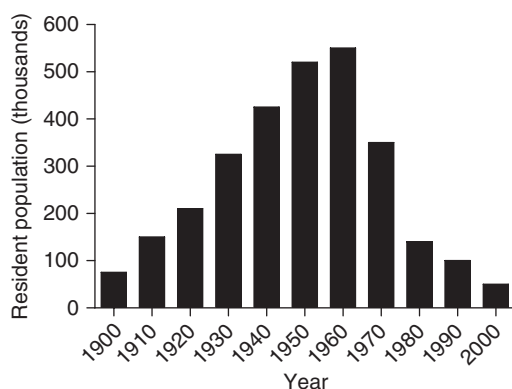


Figure 1.1 Changes in resident population in psychiatric institutions in the United States during the twentieth century. (Adapted from Manderscheid *et al.*, 2009. Copyright © 2009, Vendome Healthcare.)

treatments that are mechanistically driven can be developed. For example, Type 1 diabetes mellitus is a disease where there is a deficiency of the pancreatic hormone, insulin. The function of this hormone is to facilitate the uptake of the glucose from the blood and into the tissues. The consequences of a lack of this hormone are that the levels of glucose in the blood rise to a potentially life-threatening level, and the tissues of the body are starved of glucose, the major source of energy. The body responds by having to utilise other sources of energy (such as breaking down protein into amino acids), resulting in the wasting aspects of the disease. Administration of insulin in a fashion that mimics the natural secretory patterns will result in a normalisation of plasma glucose levels by removing glucose from the blood and a consequent amelioration of the symptoms of the disease. If only things could be so straightforward in the pharmacological treatment of CNS disease!

1.1 The global burden of CNS disease

Assessing the burden that disease places on a society is an enormous challenge, but one that is vitally necessary to allow governments to gauge the magnitude of health problems that they currently face, as well as trying to make reasonable predictions about the shifting nature of these health problems into the future, i.e. in the absence of any interventions on their part. Most diseases that are not the result of either infections or cancer can be considered to be ‘incurable’. This means that the goal of therapy involves treating the symptoms, without being able to cure the underlying biological changes that are present in the sufferer of the disease. Using our earlier example of insulin treatment for Type 1 diabetes mellitus, this pharmacological treatment strategy will allow the patient to live a largely normal life with little

outward signs of the disease. However, if the insulin treatment were to be discontinued at any time during their life, the symptoms of the disease would re-emerge; thus, diabetes mellitus is a lifelong disease whose symptoms can be controlled pharmacologically.

CNS disorders can be thought to be of a similar nature. Bipolar disorder, epilepsy and schizophrenia are CNS disorders that have usually presented during childhood or adolescence and are lifelong illnesses. Depression and anxiety disorders can also be of a lifelong nature, but can be precipitated at any stage, and may be of a transient nature, i.e. an episode occurring during one's life with no further recurrence. Alzheimer's and Parkinson's disease are typically of a late onset in life. There are some CNS disorders that are absolutely 100% genetically determined, which have been inherited and programmed to manifest themselves at a certain age, such as Huntington's disease and some genetic forms of Alzheimer's and Parkinson's diseases. Cerebrovascular stroke is a condition that afflicts the brain (it can be considered as analogous to an ischaemic attack of the heart), due to a specific cardiovascular event, and as such is the only condition that afflicts the brain, where the cause can be defined. However, the damage that occurs in the immediate aftermath of such a cerebrovascular event (i.e. the 'therapeutic window') means that the scope for pharmacological intervention is limited to this period.

1.2 Assessment of the global burden of disease

As mentioned earlier, assessment of the magnitude of disease plays a vital role in making decisions and formulating policy on health issues. To this end, the World Health Organization (WHO) produced its first Global Burden of Disease (GBD) study in 1990, where it acquired statistics on the incidence of more than 100 diseases and injuries, examining the morbidity and mortality associated with these diseases from a global, but also regional, perspective. An update of this GBD study has taken place for 2004 (WHO, 2008). In this study, CNS disorders come under the umbrella term 'neuropsychiatric disorders' and for convenience can be divided into three broad categories:

- *Psychiatric conditions*: Unipolar depressive disorders; bipolar affective disorder; schizophrenia; post-traumatic stress disorder; obsessive-compulsive disorder; panic disorder; insomnia
- *Neurological/neurodegenerative conditions*: Epilepsy; Alzheimer's disease and other dementias; Parkinson's disease; multiple sclerosis; migraine
- *Substance abuse conditions*: Alcohol-use disorders; drug-use disorders.

The total number of deaths from any cause has been estimated worldwide to have been nearly 59 million in 2004. Of these, 2.1% (or 1.26 million) were attributed to neuropsychiatric disorders. The breakdown of these deaths by CNS disorder type is depicted in Figure 1.2.

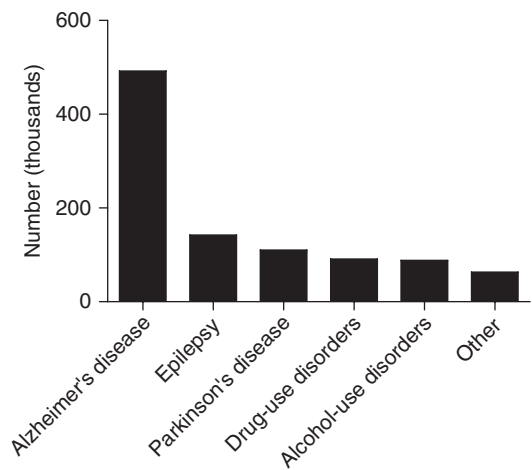


Figure 1.2 Estimates of global deaths caused by CNS disorders, 2004. Alzheimer’s disease also includes other dementia types. Within the ‘Other’ category, unipolar depressive disorders (15 000), schizophrenia (30 000) and multiple sclerosis (17 000) are the main contributors. (Data derived from WHO (2008).)

From a burden perspective, the report uses various measures. These include the sum of years lost to premature mortality (YLL), the years lost to disability (YLD), and the disability-adjusted life years (DALYs), which we will discuss further later. The report has ranked diseases and conditions according to the magnitude of the disability associated with them. These disability classes are summarised in Table 1.1 and range

Table 1.1 Disability classes for certain CNS disorders

Disability class	Severity weight	Example
I	0.00–0.02	Stunting due to malnutrition
II	0.02–0.12	Amputated finger
III	0.12–0.24	Angina
IV	0.24–0.36	Congestive heart failure, Parkinson’s disease
V	0.36–0.50	Mild mental retardation, bipolar disorder
VI	0.50–0.70	Blindness, Alzheimer’s disease and other dementias
VII	0.70–1.00	Terminal stage cancer, active psychosis, severe depression

The severity weights range from 0 (perfect health) to 1 (death). They represent an average for each condition, which itself can potentially span several (if not all) disability classes. (Taken from WHO (2008).)

in severity across seven levels. The first disability class is a relatively modest form of disability that would have little impact on an individual's quality of life. However, the seventh disability class is one that is so severely disabling that it can be considered to be, at its most extreme, life-threatening. With regard to CNS disorders, it can be seen that they have a representation in several of the more severe disability classes. Thus, using this particular classification system, we can see that certain CNS disorders are extremely disabling, some of which are on a par with the terminal stages of cancer.

1.3 The prevalence of CNS disorders

Table 1.2 consists of the prevalence of certain CNS disorders across the world, and also in its regions. It can be seen that depression (i.e. unipolar depression) is the most prevalent CNS disorder worldwide, followed by epilepsy, bipolar disorder, schizophrenia, Alzheimer's disease and Parkinson's disease.

Table 1.2 Global and regional prevalence (millions) of certain CNS disorders

Disorder	World	Africa	America	E. Med	Europe	S.E. Asia	W. Pacific
Depression	151.2	13.4	22.7	12.4	22.2	40.9	39.3
BPD	29.5	2.7	4.1	2.1	4.4	7.2	8.9
Schizophrenia	26.3	2.1	3.9	1.9	4.4	6.2	7.9
Epilepsy	40.0	7.7	8.6	2.8	4.1	9.8	7.0
AD	24.2	0.6	5.0	0.6	7.6	2.8	7.4
PD	5.2	0.2	1.2	0.2	2.0	0.7	1.0
Alcohol disorders	125.0	3.8	24.2	1.1	26.9	21.5	47.3

BPD = bipolar disorder; AD = Alzheimer's disease and other dementias; PD = Parkinson's disease. (Taken from WHO (2008).)

1.4 Disability due to CNS disorders

1.4.1 YLD as an indicator of extent of disability

As part of the GBD 2004 study, WHO has prepared a table of the 10 leading causes of death, broken down by gender, from which the CNS disorders that are represented are depicted in Table 1.3. As can be seen, three neuropsychiatric (namely unipolar depression, schizophrenia and bipolar disorder) conditions are represented in the top 10 leading causes of years lost due to disability, with unipolar depression being ranked first, irrespective of gender. When broken down according to gender, the YLD due to unipolar depression is much greater in females than in males. Overall, neuropsychiatric conditions are the most important single cause of disability across

Table 1.3 CNS disorders that are amongst the leading global causes of YLD in 2004

Cause	Total YLD	Male	Female
Unipolar depression	65.3	24.3 (1)	41.0 (1)
Schizophrenia	16.3	8.3 (5)	8.0 (6)
Bipolar disorder	14.4	7.3 (7)	7.1 (8)

The figures are expressed in millions. YLD = years lost due to disability. Numbers in brackets are the ranking of the disorder within the particular gender. (Taken from WHO (2008).)

all regions of the world population aged 15 or over. There are other CNS conditions that are represented, but only in one of the genders. For example, alcohol-use disorders are the second most important cause of YLD in males, whilst Alzheimer's disease and other dementias are ranked 10th in the female category.

Another way in which the YLDs have been examined is by dividing the world into either low/middle-income countries or high-income countries (Table 1.4). Here, we can see that unipolar depression is still the major cause of YLD irrespective of income, but that schizophrenia and bipolar disorder are more prevalent in low-and middle-income countries, whilst Alzheimer's disease and other dementias are the 4th leading cause of YLD in high-income countries; alcohol abuse is high up the list of YLDs for both categories.

Table 1.4 CNS disorders that are leading causes of YLD according to relative wealth of countries

Low/middle-income countries		High-income countries	
Cause	YLD	Cause	YLD
Unipolar depression (1)	55.3	Unipolar depression (1)	10.0
Alcohol-use disorders (4)	18.4	Alcohol-use disorders (3)	3.9
Schizophrenia (6)	14.8	Alzheimer/other dementias (4)	3.7
Bipolar disorder (8)	12.9	Drug-use disorders (10)	1.7

The figures are expressed in millions. YLD = years lost due to disability. Numbers in brackets are the ranking of the disorder within the top 10 causes. (Taken from WHO (2008).)

1.4.2 DALYs

According to WHO (2008), measuring the incidence, prevalence and YLD do not themselves give an accurate depiction of the burden placed upon society by disease. They have developed the concept of the disability-adjusted life year

(DALY) which ‘can be thought of as a measurement of the gap between current health status and an ideal situation where everyone lives into old age, free of disease and disability’ (WHO, 2008). The DALY is a combination of the YLL (years of life lost due to premature death) and the YLD (equivalent healthy life years lost through living in states of less than full health due to disease and injury). When the DALYs are calculated, unipolar depressive disorders are ranked third in total number, with 65 million DALYs, with only lower respiratory infections (94.5 million DALYs) and diarrhoeal diseases (72.8 million DALYs) being ranked ahead of them. This list is dominated by infectious diseases, birth and congenital abnormalities, and injuries of one type or another. When middle-income and high-income countries are considered, unipolar depressive disorders are the leading cause of DALYs, with Alzheimer’s disease and other dementias coming 4th in high-income countries. When looking into the future, it is predicted that unipolar depressive disorders will be the leading cause of DALYs worldwide by 2030. The estimated global DALYs for neuropsychiatric disorders for 2004 have been estimated at 200 million (approx 13% of the total DALYs). The breakdown of these DALYs according to disease type is depicted in Figure 1.3.

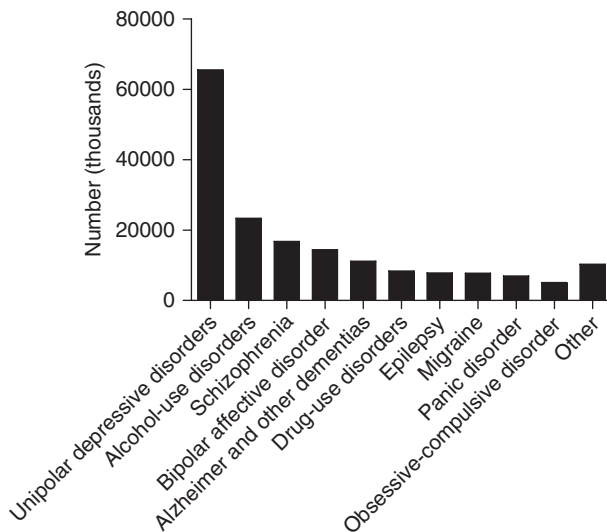


Figure 1.3 Global DALYs estimate for neuropsychiatric disorders, 2004. Data are the 2004 estimates for disability-adjusted life years (DALYs) adapted from WHO (2008). Within the ‘Other’ category are insomnia (3623), post-traumatic stress disorder (3468), Parkinson’s disease (1710) and multiple sclerosis (1527)

1.4.3 Regional distribution of DALYs

The three categories of neuropsychiatric conditions (namely psychiatric, neurological/neurodegenerative and substance abuse) have been summarised in Table 1.5, according to regional distribution. The total number of DALYs for each region are roughly in keeping with their population, but when subdivided into different categories reveal some regional differences in prevalence. For example, substance-abuse disorders have a lower prevalence of DALYs in Africa and south-east Asia, and a greater prevalence in the Americas and Europe than would be expected based on population. Also, psychiatric disorders have a greater prevalence in south-east Asia, whilst neurological/neurodegenerative disorders are more prevalent in Europe and the Americas.

Table 1.5 Regional distribution of DALYs for neuropsychiatric disorders

Region	Population (millions)	Total Neuropsych. DALYs (thousands)	Psychiatric (thousands)	Neuro/ Neurodegen. (thousands)	Subst. Abuse (thousands)
World	6437	177 659	115 652	29 960	32 047
Africa	738 (11%)	15 611 (9%)	10 935 (9%)	2948 (10%)	1728 (5%)
S.E. Asia	1672 (26%)	47 228 (27%)	35 032 (30%)	6692 (22%)	5504 (17%)
Americas	874 (14%)	29 974 (17%)	17 437 (15%)	5274 (18%)	7263 (23%)
E. Med.	520 (8%)	13 568 (8%)	9834 (9%)	1790 (6%)	1944 (6%)
Europe	883 (14%)	26 412 (15%)	14 340 (12%)	5703 (19%)	6369 (20%)
W. Pacific	1738 (27%)	44 866 (25%)	28 074 (24%)	7553 (25%)	9239 (29%)

Data derived from WHO (2008). The DALYs for a range of CNS disorders have been divided into psychiatric, neurological/neurodegenerative and substance abuse. The percentage of the total for each category is in brackets.

1.5 Economic Costs

As well as the burden of CNS disease being expressed in terms of years lost due to early mortality, morbidity or disability, there have also been attempts to calculate the economic burden, i.e. the financial costs of the disease. The measures used have proven to vary enormously from one study to another due to marked differences in the study design and cost model utilised. For example, some studies have generated figures based purely on calculating the direct costs of the disorder, i.e. in its treatment.

Other studies have attempted to estimate the total costs, i.e. both the direct costs and the indirect costs. Direct costs include hospital care, drugs outpatient care and social services, and have been estimated on average for CNS disorders to be 53%, with the drug costs representing only 3% of these costs (Andlin-Sobocki *et al.*, 2005). The remaining 47% is made up of sick leave (33%), early retirement (7%) and premature death (7%). Notwithstanding these challenges, for the United States, Eaton *et al.* (2008) have prepared an economic cost for neuropsychiatric diseases based on 2005 US\$ figures, derived from a variety of sources. These figures are summarised in Figure 1.4. It can be seen that the cost estimates are staggering, with substance-abuse disorders combined having a cost of over US\$400 billion p.a. (with much of this figure related to the cost of criminal activities linked to these disorders), whilst unipolar depressive disorders are estimated at close to US\$100 billion p.a. and the other four listed conditions estimated at between US\$68 and US\$79 billion p.a. The total for the seven disorders in Figure 1.4 comes to over US\$800 billion. Such a burden is far greater than that estimated for diabetes in the USA at US\$174 billion p.a. in 2007 (American Diabetes Association, 2008), and for cancer, which is estimated in the USA at US\$206 billion p.a. in 2006 (American Cancer Society, 2007).

In Europe, there has been an extensive examination involving the 25 EU countries, as well as Iceland, Norway and Switzerland, where costs have been estimated for a range of CNS disorders for each country. Table 1.6 summarises

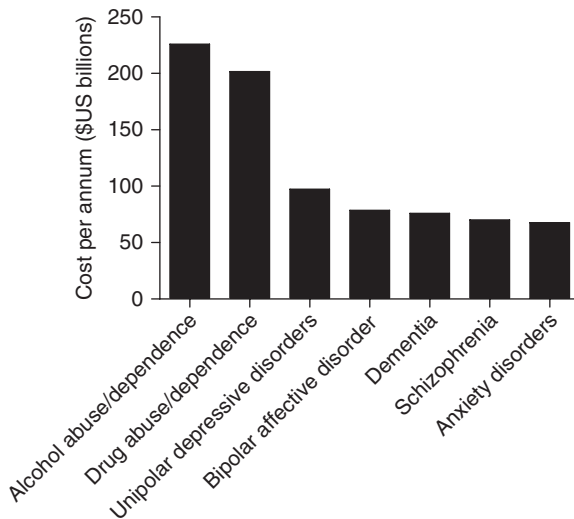


Figure 1.4 Economic costs of CNS disorders in the United States. Anxiety disorders include panic disorder, social phobia, simple phobia and obsessive-compulsive disorder. The costs are in US\$ per annum, based on 2005 figures. (Taken from Eaton, W. W., Martins, S. S., Nestadt, G., Bienvenu, O. J., Clarke, D. and Alexandre, P. (2008). The burden of mental disorders. *Epidemiol. Rev.*, **30**, 1–14 and reproduced by permission of Oxford University Press.)

Table 1.6 Average economic cost estimates of CNS disorders in Europe

Condition	Cost
Alcohol addiction	€5836 (€1559 – €10 463)
Drug addiction	€3823 (€1174 – €6899)
Anxiety disorders: GAD	€1804 (€531 – €3238)
OCD	€350 (€90 – €617)
Panic	€967 (€242 – €1703)
Specific phobia	€517 (€133 – €914)
Agarophobia	€941 (€225 – €1650)
Social phobia	€937 (€248 – €1662)
Unipolar depressive disorder	€3826 (€952 – €7102)
Bipolar depressive disorder	€6081 (€1492 – €10 412)
Schizophrenia	€7688 (€2360 – €13 862)
Dementia	€10 722 (€3265 – €19 480)
Parkinson's disease	€7577 (€2533 – €12 996)
Epilepsy	€5352 (€1329 – €9260)

The results are expressed as the average international euro purchasing parities per patient (€) based on 2004 figures. The values in brackets represent the absolute range between the 28 countries (the 25 EU countries, plus Iceland, Norway and Switzerland). (Adapted with permission from Andlin-Sobocki *et al.*, *Eur. J. Neurol.* (2005), 12, 1–27. Copyright 2005 Blackwell Publishing.)

the average cost per patient of certain CNS disorders in the EU, along with the ranges found across countries. As can be seen, there is a considerable variation in the cost per patient, which may not be surprising when we consider the diversity in economies that are present in Europe, and the consequent wide variation in resource provision across countries (Knapp *et al.*, 2002). From these results, there is considerable variation in the average costs for CNS disorders, with dementia, schizophrenia and Parkinson's disease being the most costly, whilst most of the anxiety disorders are the least costly. This variation can be attributed to the disabling nature and intensive medical and nursing treatment that is required for the neurodegenerative diseases and schizophrenia, when compared to the anxiety disorders.

These costs have also been estimated as a total economic burden, in a similar fashion to that described previously for the United States, and summarised in Figure 1.5. The total cost for the five clusters of CNS disorders depicted is over €300 billion p.a., with the affective disorders (i.e. unipolar and bipolar depressive disorder) representing the single biggest cluster (Andlin-Sobocki *et al.*, 2005).

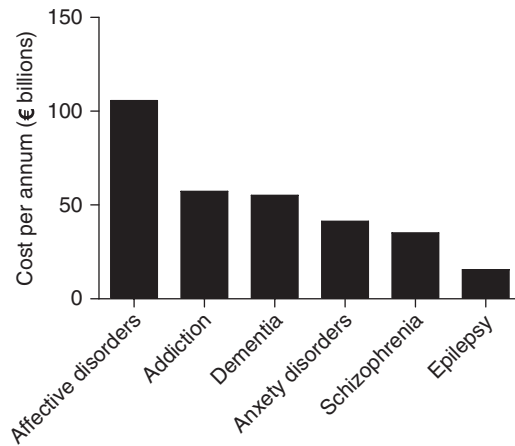


Figure 1.5 Economic costs of CNS disorders in Europe. (Adapted with permission from Andlin-Sobocki *et al.*, *Eur. J. Neurol.* (2005), **12**, 1–27. Copyright 2005 Blackwell Publishing)

1.6 Concluding comments

This chapter has highlighted the burden that CNS disorders represent. Such disorders are extremely prevalent in all societies, regardless of the stage of their economic development. However, not surprisingly, diseases which are mainly of an older-age onset, such as Alzheimer's disease and Parkinson's disease, have a greater prevalence in the developed world. However, such diseases will become more prevalent as the global population profile has a larger representation of older people. Many CNS disorders are severely disabling, resulting in great suffering for those afflicted with the disease, as well as their families, and being often a source of premature death. With this in mind, there have been estimates made of the economic cost of CNS disorders, most particularly in Europe and the USA, which can be counted in hundreds of billions of euros and dollars per annum. Thus, the burden is immense and the search for effective treatments that can reduce or eliminate the disabling aspects of CNS disorder is a major global healthcare imperative. The role that drug treatment can play will form the basis of this book.

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