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HEALTH ECONOMICS OF DEPRESSION

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*For everything there is a season, and
a time for every matter under heaven
Eccles 3:1*

ABSTRACT

Health economics deals with how resources are used for health production and how they should be most efficiently allocated to maximise health outcomes. Many treatment alternatives for depression are currently available, but there is insufficient knowledge of their consequences on costs and their value of actual and potential health gains. The aims of the present thesis were to study aspects of the health economics of depression that are important for priority settings: the burden of depression to society, cost and health-related quality of life associated with patients treated for depression and modelling the cost-effectiveness of treatments for depression.

A new approach was developed to assess the societal cost of depression in Europe. The results showed that more than 21 million Europeans are suffering from depression and that depression cost European society more than SEK 1 000 billion per year, two-thirds of which are found outside the healthcare system. The cost of depression equals SEK 2 300 per inhabitant in Europe corresponding to 1% of the European national incomes.

Naturalistic studies of cost and outcome in clinical practice are rare. The study "Health Economics of Depression In Sweden" (HEADIS) is one of the first naturalistic observational studies conducted in Sweden, collecting information on the cost and quality of life related to patients treated for depression in primary care. The cost for a patient treated for a depressive episode was estimated at SEK 51 000. Depressed patients were, on average, absent from work 1.5 months during six months, which constituted 65% of the total costs for depression. Depression causes a reduction in quality of life of 50% as compared to the general population, which is in the same range as after a severe stroke. Treatment significantly improved patients' quality of life measured with a standard generic quality of life instrument (EQ-5D). For patients who went into remission, we observed both statistically significant reductions in costs and improvements in quality of life of more than 40% as compared to non-remitting patients.

A computer simulation model was developed to project costs and benefits from alternative treatments for depression. The health economic data collected in the HEADIS study was used in the model. A simulation was performed with a hypothetical intervention over a five-year period. The results showed that a new treatment which increases the probability that the patient goes into remission, produced cost savings amounting to SEK 20 100 and a QALY gain of 0.07. The results underscore that the achievement of clinical remission is a key health economic parameter to reduce the burden of depression.

This thesis has contributed with new health economic data on the social cost of depression at an international level, and patient-level data of costs and quality of life for depressed patients in a primary care setting. Accurately estimating the impact of a disease, in terms of costs and quality of life, is the first important step towards better priorities of resource allocation to reduce the burden of the disease. This data is also an input in economic evaluations, which provides information for allocation of resources between different types of treatments. Increased research efforts are needed to provide the necessary effectiveness data in clinical practice, and to make such studies relevant and credible as instruments for resource allocation in practice.

Key words: depression, cost of illness, cost, quality of life, cost-effectiveness, modelling

LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred to by their Roman numerals:

- I. Sobocki P, Angst J, Jönsson B, Rehnberg C (2006) Cost of depression in Europe. *Journal of Mental Health Policy and Economics*. 9: 87-98.
- II. Sobocki P, Ekman M, Ågren H, Runeson B, Krakau I, Mårtensson B, Jönsson B (2006) Resource-use and costs associated with patients treated for depression in primary care. *In press, European Journal of Health Economics*.
- III. Sobocki P, Ekman M, Ågren H, Runeson B, Krakau I, Mårtensson B, Jönsson B (2006) Health-related quality of life measured with EQ-5D in patients treated for depression in primary care. *In press, Value in Health*.
- IV. Sobocki P, Ekman M, Ågren H, Runeson B, Jönsson B (2006) The mission is remission - health economic consequences of achieving full remission with antidepressant treatment for depression. *International Journal of Clinical Practice*. 60(7):791-8.
- V. Sobocki P, Ekman M, Ågren H, Jönsson B, Rehnberg C (2006) A model to assess the cost-effectiveness of antidepressant treatment in depression. *International Journal of Technology Assessment in Health Care*. 22(4): 469-477.

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LIST OF ABBREVIATIONS

A&E	Acute and emergency
ANOVA	Analysis of variance
CBT	Cognitive behavioural therapy
CGI-I	Clinical global impression improvement scale
CGI-S	Clinical global impression severity scale
CI	Confidence interval
DALY	Disability-adjusted life year
DDD	Defined daily doses
DSM	Diagnostic and statistical manual of mental disorders
ECT	Electroconvulsive therapy
EQ-5D	EuroQol 5 dimensions
GDP	Gross domestic product
HAM-D	Hamilton depression scale
HEADIS	Health economics aspects of depression in Sweden
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICD	International classification of diseases
IPT	Interpersonal psychotherapy
KW	Kruskall-Wallis
LYG	Life-years gained
MADRS	Montgomery-Asberg depression rating scale
MAOI	Monoamine oxidase inhibitor
MAU	Multi attribute utility
MPT	Maintenance pharmacotherapy
PPP	Purchasing power parity
QALY	Quality-adjusted life year
QoL	Quality of Life
RIMA	Reversible inhibitor of monoamine oxidase
SD	Standard deviation
SEK	Swedish kronor
SNRI	Selective norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
WHO	World Health Organization
WTP	Willingness to pay

INTRODUCTION

Depression is one of the most common reasons for mental ill health in the world, and is the most burdensome disease in Europe in terms of Disability-Adjusted Life Years [1]. The World Health Organization concludes that depression is the fourth most burdensome disease in the world [2]. Hence, depressive illness is a major global public health concern and in order to meet the needs of the people afflicted it is important to make wise decision on how health care budgets should be used for prevention, treatment and management of depression.

We live in a world of scarce resources. How these scarce resources should be optimally allocated to provide maximum output is the essence of the economic sciences. Health economics is the application of the theory of economics on health, and informs us about how we should best use our resources to produce health. Health economic evaluation is a method for assessing costs and benefits of alternative strategies of allocating resources, to assist in decisions aiming at improving efficiency. An efficient allocation of resources implies that no further health gains can be achieved by allocating resources differently.

As novel medical technologies are developed it is important to assess whether they offer good value for money as compared to older technologies. Currently, there are several treatments available for the prevention and treatment of depression. Even more interestingly there is a growing understanding of the brain in general and the nature of depression in particular, which may lead to new medical breakthroughs. New medical treatments for depression often come at high prices, which have lead to a growing concern about increasing health care budgets (especially the cost of pharmaceuticals). The increasing availability of new expensive treatments and the limited sources of funds within the health care systems have lead to a growing need for prioritising. Evidence-based medicine and economic evaluations have become important tools for assisting in decisions about resource allocation within health care. There has now been an increase in the demand for a more efficient use of the care for depression and therefore health economic studies have become increasingly important in the field.

The present thesis studies aspects of the health economics of depression that are important for priority settings: the burden of depression to society, cost and health-related quality of life associated with patients treated for depression and modelling of cost-effectiveness of treatments for depression. Below a background is provided on the disease and treatments available for depression today. Moreover, a brief introduction to the theoretical framework of health economics is presented.

Depression

Diagnosis, epidemiology and pathology

Two common diagnostic manuals used in clinical practice are the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) developed by the WHO. They have converged during the last decade and the last versions of the two manuals, ICD-10 [3] and DSM-IV [4], are very similar in their criteria for diagnosing depression. The DSM-IV provides a number of criteria for the diagnosis of Major Depressive Disorder (MDD). The patient feels loss of interest (or pleasure) in nearly all activities, accompanied by at least five of the following specific criteria during at least two weeks:

- 1) Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)
- 2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day, as indicated either by subjective account or observation made by others. Does not include symptoms clearly due to general medical condition or mood-incongruent delusions or hallucinations
- 3) Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month) or a decrease or increase in appetite nearly every day
- 4) Insomnia or hypersomnia nearly every day
- 5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
- 6) Fatigue or loss of energy nearly every day
- 7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- 8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
- 9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide due to one or more episodes that are two weeks or longer.

Moreover, the symptoms must cause clinically significant distress and/or impairment in social, occupational, or other important areas of functioning. Major depressive disorder is, however, not present if the symptoms meet the criteria for a mixed episode, or are due to the direct physiological effects of a substance or a general medical condition. Furthermore, the symptoms must not be due to bereavement, i.e. after the loss of a loved one.

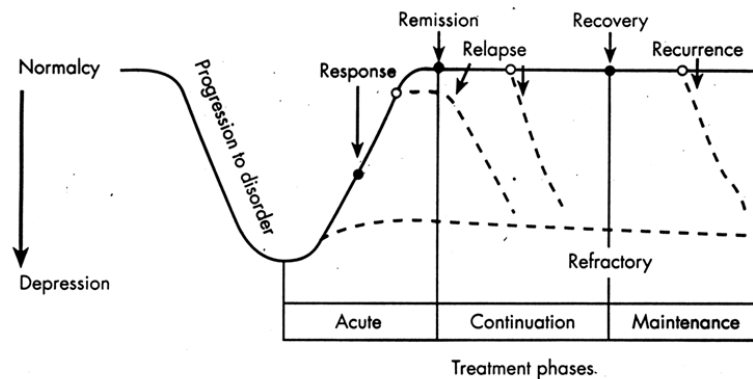
The severity of the depression is commonly assessed with rating scales. In mild depressive episodes the patient is generally able to pursue her daily activity, whereas it becomes more difficult in more severe cases. In a severe depressive episode, the sufferer usually shows considerable distress or agitation, unless retardation is a marked

feature. Loss of self-esteem or feelings of uselessness or guilt are likely to be prominent, and suicide is a distinct danger in particularly severe cases of depression.

Most epidemiological studies on depressive disorders have been conducted in randomised population surveys and are mainly focused on the working population. Depression is a common disorder all over the world, with a point prevalence between 4% and 10% [5]. Prevalence figures of up to 15% have been found in primary care [6]. Depression is twice as prevalent in women as compared to men [7]. The reasons for this probably include both social and biological factors, and differential acknowledgement of the disease. A well-known Swedish epidemiology survey is the Lundby study [8], where a cohort of 2 500 patients were surveyed for psychiatric disorders at several points in time during the twentieth century. It has been found that every fourth man, and every second woman runs the risk of getting a depression over a lifetime [9]. With repeated surveys of the Lundby cohort, there seems to be a rather stable trend in the incidence of depression over time [10]. The frequency of depression varies with age in a curvilinear manner, starting to rise in adolescence, peaking in middle age and then falling off [11]. A rise in late old age has been suggested but has not yet been clearly established [12].

Until a couple of decades ago, there was little consensus around the terminology and description of the pathology of the depressive episode and the long-term consequences of the disease. Kupfer et al [13] published a landmark article with a common set of terminology for the pathology of depression, which is becoming increasingly established. A depressive episode is the natural progression to disorder with an approximate length of six months. Once the patient returns to a symptom-free state, she experiences a *remission* from the depressive episode. A patient without depressive symptoms for six to twelve months has *recovered* from the depression. If the patient returns to the episodic phase of the disease within a relatively short period of time after remission, this is termed a *relapse*. On the other hand, if the patient returns to a depressive episode after recovery, it is called *recurrence* (Figure 1). There is no biological distinction between relapse and recurrence but, typically, there are residual symptoms remaining at a relapse, whereas the patient is symptom-free prior to a recurrence.

Figure 1 Pathology of a depressive episode



Source: Adapted from Kupfer et al [13]

The use of rating scales in clinical research in depression increased in the late 1950s with the introduction of antidepressants. To evaluate the effectiveness of these new drugs in clinical trials, it became important to use instruments with a sufficiently high degree of reliability and validity. The rating scale most widely used in the 1960s and 1970s was the Hamilton Depression and Anxiety Scales (HAM-D) [14]. With the introduction of the evidence-based diagnostic systems (beginning with DSM-III) in the 1980s, with symptom-derived diagnoses for mental disorders, an association between the symptom-oriented rating scales (e.g. HAM-D) and the clinical diagnoses emerged. In the late 1970's, Montgomery and Åsberg developed a new symptom rating scale: Montgomery-Åsberg Depression Rating Scale (MADRS) [15].

HAM-D was designed to measure the severity of depressive symptoms in patients with primary depressive illness. The most commonly used HAM-D scale is the 17-item version. HAM-D is also useful for monitoring changes in depressive symptoms during treatment and in comparing the efficacy of various interventions. MADRS contains 10 items examining common symptoms for depression. MADRS is widely used in drug-treatment trials because of its sensitivity to treatment effects. The following mean scores correlated with global severity measures: very severe 44; severe 31; moderate 25; mild 15; and recovered 7. The maximum score is 60.

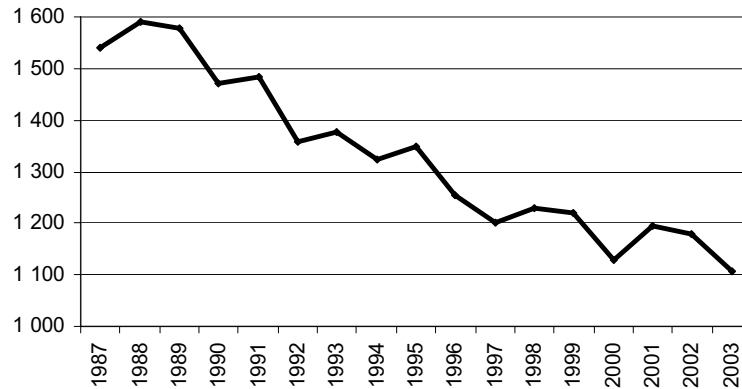
Global scales have mainly been used as observer scales to measure global symptomatology within the group of patients being assessed, e.g. the Clinical Global Impression Scale of Severity (CGI-S) [16]. During clinical trials global scales covering the change in symptomatology over time, (e.g. Clinical Global Impression Scale of Improvement [CGI-I]) have often been used.

Over the last decades, self-rating scales have been developed not only to include symptoms but also scales covering social aspects. Some of the more commonly used self-rating scales are the Beck Depression Inventory (BDI) and the Major Depression Inventory (MDI).

Morbidity and mortality

Suicide is recognized as a major public health problem and the number of suicides in Sweden amounted to around 1 100 in 2003. The majority of suicides are associated with depression [17, 18]. Suicide ideation is common among depressed patients, and 10-20% of those with ideation actually commit suicide [19]. Preventive and effective measures to decrease both suicidal ideation and suicides are therefore important [17]. The suicide rates have been reduced by almost 40% since 1987 (Figure 2). Likely reasons for this reduction are improved diagnosis setting and improved treatments for depression (e.g. antidepressants). The use of antidepressants increased seven-fold (measured in DDDs) during the same time period (Figure 2).

Figure 2 Number of suicides in Sweden (1987-2003)



Source: Data extraction from Swedish National Board of Health and Welfare [20]

Depression also has a negative impact on working ability and productivity [21-23]. Especially, it has been shown that sick leave absence (short-term and long-term) from work is common in depressed patients. The expenses of sick leave due to psychiatric disorders were estimated at SEK 8.4 billion in 2001 in Sweden, the majority of which can be attributable to depression [24]. The number of people in early retirement reached almost 490 000 in Sweden in 2002, and has increased by more than 30% since 1990. Psychiatric disorders constituted 30% of the total number of early retirements in 2002 [25], the majority of which are assumed to be due to depression. As opposed to early retirements due to other diagnoses, the prevalence of early retirements due to psychiatric disorders is found in the younger ages.

Treatments

Treatments for depression are either pharmacological or non-pharmacological. The most commonly used therapies are:

- 1) antidepressant therapies
- 2) psychotherapy
- 3) other therapies

Antidepressant therapies

Antidepressants work by increasing the amount of neurotransmitters active in the synapses, enhancing neuronal activity and increasing the responsiveness of mood. Modern antidepressants usually achieve this effect by blocking the transporter proteins that reabsorb certain neurotransmitters, named "reuptake inhibitors" [26]. Older medications, like tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) affect all neurotransmitters unselectively. These medications have the disadvantage of causing unpleasant side effects, e.g. somnolence, weight gain, and dry mouth which, in turn, may lead physicians to reduce dosages, and patients to dis-

continue treatment too early. Newer antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are more selective and have reported somewhat more advantageous adverse effect profiles.

Selective serotonin reuptake inhibitors (SSRI). Newer medications, like selective serotonin reuptake inhibitors (SSRIs), affect neurotransmitters selectively [26]. The main advantage of these antidepressants is that they generally have less severe side effects; hence improved tolerability. Apart from SSRIs, there are several new selective antidepressants, e.g. reversible inhibitors of monoamine oxidase A (RIMAs), which also have fewer side effects than TCAs. However, treatment effects may be difficult to predict and a patient who does not respond to one type of treatment may respond to another.

Tricyclic antidepressants (TCA). Tricyclic antidepressants, the first widely used class of antidepressants, act by blocking reuptake of neurotransmitters (serotonin and norepinephrine) presynaptically so that more of them are available for transmission of electrical impulses [26]. As with most antidepressants, TCAs may cause anticholinergic side effects, including dry mouth, urinary retention, postural hypotension, blurred vision and constipation.

Monoamine oxidase inhibitors (MAOI). MAOIs act by inhibiting monoamine oxidase, an enzyme, from transforming neurotransmitters into metabolites, and increasing the number of enzymes for transmission [26]. The side effects of MAOIs are not unlike those of the TCAs, but patients on MAOIs must adhere to a diet for tyramine control to prevent hypertensive crises. Newer MAOIs, with a reversible and selective inhibitor, reversible inhibitor monoamine A (RIMA) isoenzyme, are available with a somewhat advantageous adverse effect profile.

Other antidepressants. Among other antidepressants, *serotonin-norepinephrine reuptake inhibitors* (SNRI) [26] are most commonly used. SNRI drugs were developed more recently than SSRIs, and they are relatively few. SNRIs have an activity on epinephrine reuptake which is a property shared with the older tricyclic antidepressants but not with the SSRIs. SNRIs have little or no anticholinergic effects but may interfere with sexual function.

Psychotherapy

Psychotherapy is an alternative to drug treatments, and include *cognitive therapy*, *behavioural therapy*, *cognitive behavioural therapy* and *inter-personal therapy*. Such approaches have been shown to be effective in a range of cases. Although psychotherapy and drug therapy were traditionally considered as mutually exclusive, combinations of the two are commonly used. Several forms of short-term psychotherapy have been shown to be as effective as pharmacotherapy in treating most cases of major depression [27-29]. There is strong support for psychotherapy being an effective treatment in mildly and moderately depressed patients [26].

Other therapies

Other types of treatments available for depression include *electroconvulsive therapy (ECT)*, *light therapy* and *St John's Wort*. *ECT* is a psychiatric shock therapy involving

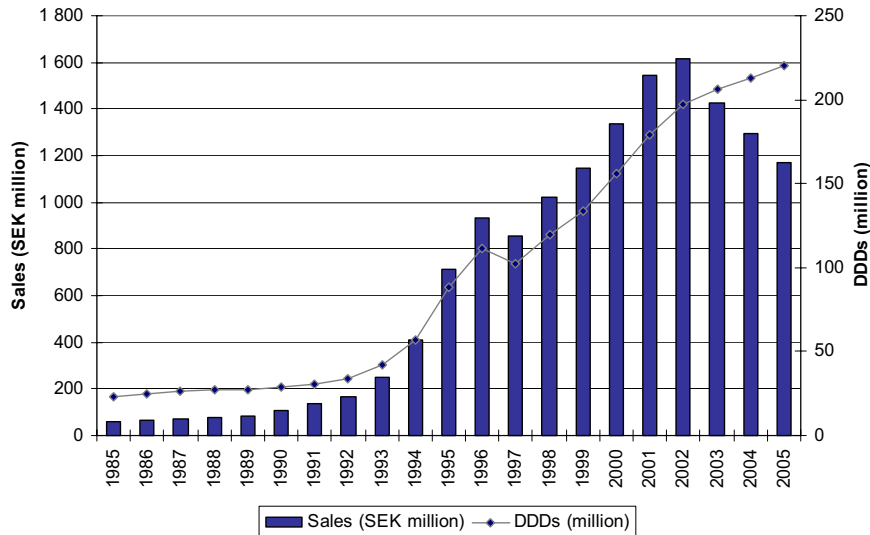
the induction of a seizure in a patient by passing electricity through the brain. *ECT* is usually reserved for very severe or psychotic depression or manic states that often do not respond to pharmacotherapy. *Light therapy* has mainly been used for seasonal affective disorder, but there is still little evidence for its effectiveness [26]. Treatment with *St John's Wort* has a long tradition, and the treatment is based on extracts from *St John's Wort*. It has antidepressant properties, but the effect of the active substance in *St John's Wort* is, however, not isolated in the pharmaceutical preparations of the treatment.

Other less common methods for treating depression are *Transcranial Magnetic Stimulation (TMS)* and *Vagus Nerve Stimulation (VNS)*. *TMS* is a rather new technology, which uses powerful rapidly changing magnetic fields to induce electric fields in the brain by electromagnetic induction. So far, the effectiveness of the treatment remains unclear [26]. *VNS* is another new method for treating depression. It involves the implantation of a generator stimulating the vagus nerve in the brain, thus reducing seizure activity.

Use of antidepressants in Sweden

Pharmaceutical sales of antidepressants increased heavily during the 1990's (Figure 3) [30]. This increase was mainly due to the introduction of the SSRIs. Total sales have increased from 100 MSEK in the year 1990 (128 MSEK in 2005 year prices) to almost 1 200 MSEK in the year 2005, which is an increase by more than 1 100% (or 900% when adjusting for inflation). The sales peaked in 2002 (1 600 MSEK) and then dropped down to around 1 200 MSEK in 2005. The number of prescribed daily doses (DDD) has, however, been steadily increasing over time, reaching 1.6 billion DDDs in 2005, which is an increase of 600% as compared to 1990. The sales figures and DDDs follow the same pattern until the year 2002. From this year and onwards the sales figures turn down, whereas the number of drugs prescribed continues to increase. In the year 2002, a new law was passed on generic substitution. Moreover, some antidepressants went off patent in recent years (e.g. sertraline). These are likely to be the explanations for the diverging pattern of sales and DDDs (Figure 3). Today, 3.7% of the total pharmaceutical sale in Sweden can be related to antidepressant treatments. The sales figures are not solely attributable to depression, since it is difficult to separate the drugs prescribed for depression from other indications.

Figure 3 Sales and volumes of antidepressants (N06A) in Sweden 1985-2005 (sales in current prices and volumes in DDDs)

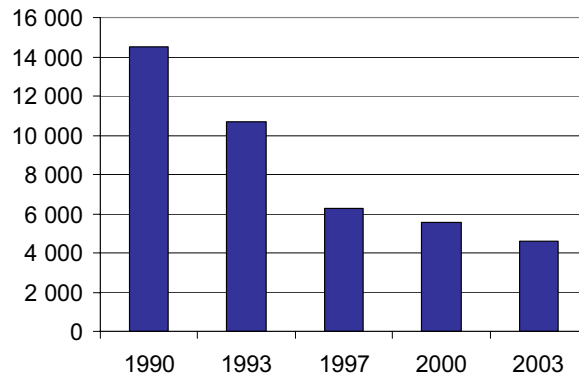


Source: Swedish Pharmacy [30]

Management of depression

A change in care for depression has been observed in Sweden over the last decades. In 1990, there were almost 15 000 psychiatric inpatient beds available, which have been reduced to less than 5 000 today (Figure 4) [31]. A number of political reforms were implemented during the 1990s, shifting the psychiatric care to the outpatient setting. The number of patients treated in psychiatric care has also decreased during the last decade; between 1998 and 2003 the decrease was 10% [31]. During the same period, the total number of days of psychiatric care decreased by more than 22%, above all due to an increased amount of admissions shorter than one day. The total number of psychiatric outpatient visits was 3.8 million in 2003, some 25% of which were visits to physicians, whereas the rest was to other health professionals in psychiatry [32]. With an expansion of psychiatric outpatient care in Sweden, community care has also increased (e.g. special living increased by 35% between 1998 and 2002) [31].

Figure 4 Average number of inpatient beds for psychiatric care over time



Source: Swedish National Board of Health and Welfare [31]

Today, various treatment alternatives are available for depression. However, there are national treatment guidelines¹. Some international guidelines with recommendations exist [33-35]. It is suggested that antidepressant treatment should be the first-line treatment for moderate and severe depression. There is, however, less conformity in the treatment of milder depressions, where patients may be offered education, support and monitoring of the depression. Moreover, there is little consensus about which antidepressants should be first-line treatment [36]. As specific antidepressants work differently with different patients, general guidelines are difficult to create. Until today, psychotherapy has mainly been considered for chronic or recurrent depressions or when the response to drug treatment has been unsatisfactory [37]. Psychological treatment is more expensive than drugs, but is not seldom a preferred treatment by patients, especially among those with milder forms of depression [38].

There is a growing understanding of the importance of detecting depression early in order to prevent a chronic progression of the disorder. Today, we have stronger evidence for antidepressant treatment preventing suicides in Sweden (especially in the younger populations) [39], and a wider portfolio of treatment strategies available, which has increased the potential of detecting depression earlier and more effectively treating the disease. Nevertheless, there is little knowledge about how treatments for depression are used in clinical practice, and there are still strong indications on both under-recognition of depression [40] as well as under-use of treatments available [41].

¹ At the time of writing the present thesis, the Swedish National Board of Health and Welfare (Socialstyrelsen) was, however, developing treatment guidelines for depression.

Health economics

Cost of illness

A cost of illness study estimates the costs related to a specific disease. This type of study provides important information about the total burden of the disease and where these costs occur in society. The cost of illness study does, however, not give direct guidance on how resources should be allocated to improve efficiency, but provides necessary information for economic evaluations.

Analysis approach

Cost of illness studies are most often based on a top-down or bottom-up approach [42]. The top-down approach means that the total national costs for illnesses are divided between different diseases according to main diagnosis. In the bottom-up approach, data are directly collected from a sample of patients with a defined disease, and the figures from the sample are extrapolated to represent the whole population by using national prevalence figures.

The advantage of using the top-down approach is that no extrapolation is necessary which avoids the risk of double counting. The disadvantage is that diagnoses may be underreported or misreported and that important cost items are often missing from the national illness registries. If a pure top-down approach is employed, costs for social services or unpaid home help are unaccounted for; since such resource use is not registered according to diagnosis. Mortality and disability pensions granted are on the other hand often recorded by main diagnoses in the national registries. Short-term sick leave statistics are, however, normally deficient or lacking, at least by diagnosis level.

Cost of illness studies can be performed either using the prevalence or incidence method [42]. Prevalence-based studies examine costs incurred during a given time-period, usually one year, regardless of the date of the onset of disease. Incidence-based studies examine costs for cases of a disease which develop for the first time in that year. Future costs and production losses are then estimated for the entire lifetime of these patients and calculated in terms of present values. As incidence-based studies can be used for calculating the economic benefits of reducing the number of new cases, they are suitable for evaluating preventive measures [43]. The prevalence method has the advantage of producing cost estimates which present the annual costs for a disease for a given year and thus, are comparable with the total annual costs for other, or all, diseases. If cost control is the primary concern, the prevalence approach is preferred, as the main components of current spending and lost resources (indirect costs) are identified, and can be subject to savings efforts.

Costs

A cost of illness study can be conducted from several different perspectives. The chosen perspective determines which costs are included in the analysis (e.g. an individual hospital, insurance company, government). The *societal perspective* implies that all costs, whether incurred by individuals, employers, or government, should be taken into account. This is preferred, since the economic theory underpinning the evaluative work in the health care field has focused on the social welfare function, which suggests a broad societal perspective. A second reason is that many diseases (particularly depression) have an impact across a wide range of personal dimensions (e.g. the individual's health, quality of life, ability to work, social relations, income etc). It would therefore be falsely constraining to only look at the health care consequences of a disease. Furthermore, the boundaries around health care differ between countries, which makes comparisons of results more difficult based on more narrow perspectives than the social perspective.

Costs are usually divided into *direct* and *indirect costs* [44, 45]. Sometimes *intangible costs* are also included in the analysis. Intangible costs are costs associated with pain, psychosocial suffering, and changes in social functioning and activities of daily living caused by the disease. The costs associated with increased life expectancy should also be included in evaluations if the intervention affects survival [46].

Direct costs include direct medical costs and direct non-medical costs. The main groups of direct medical costs are cost of inpatient (hospital) care, outpatient care (e.g. physician and nurse visits), procedures and tests, devices, and services such as home care. Direct non-medical costs (costs unrelated to health care) include e.g. the cost of transportation, adaptations, investments and services such as social assistance and unpaid care by relatives etc. [44, 45].

Indirect costs are related to productivity loss in society due to illness. Examples of indirect costs are costs of sick leave, reduced productivity at work or early retirement. Diseases mainly affecting the elderly who are no longer participating in the labour force, have no indirect costs [44, 45]. An additional type of indirect cost is the value of leisure time lost by patients with a disease (e.g. due to time spent on care seeking and transportation). Cost of leisure time has, for instance, been investigated in hypertension [47].

Intangible costs are consequences for which it is difficult to measure and assess a value. This type of cost is rarely explicitly included as a cost in an economic evaluation but more often incorporated as a utility in the denominator of the ICER.

When health care interventions prolong the life of patients there may also be a cost for society associated with the increased survival. This *cost in added life years* corresponds to the difference in consumption and production over the gained years. Such costs should be included in economic evaluation from a societal perspective [46]. The size of this cost will depend on the age of the patient. Elderly patients (in retirement) most often consume more resources than they produce while younger people produce more than they consume.

Costing

The basic principle in costing is that resources should be valued according to their “opportunity cost” (i.e. the cost in terms of opportunities lost). This means that the best alternative use for the resource should be decided and the cost of the same considered in relation to its alternative use. Since it is not possible to directly observe this opportunity cost we are, in practice, limited to the observation of “accounting costs”. An important part of any cost of illness study is to make a judgement of how well these “accounting costs” reflect the true opportunity cost.

There are three main steps in estimating costs: (1) identifying relevant resources, (2) quantifying the same and (3) valuing the costs of the quantified resources. After having defined and quantified the relevant resource use items for a disease, unit costs need to be attributed to these resources. According to economic theory, a resource should be priced based on its opportunity cost, i.e. the value of the benefits that is foregone because the resource is not available in its best alternative use [45]. However, in practice the market price of the resource is most often used.

Market prices are available for several resources but for some non-market items, such as informal care (e.g. care by family or relatives), the valuation is more problematic. Different principles can be applied when valuing informal care. One way of estimating the opportunity cost of informal care is based on the income lost due to relatives and others performing informal care [48]. The opportunity cost could then be estimated by the caregivers wage rate. However, the time spent on informal care is often also at the expense of leisure time which also has a value. The opportunity cost of lost leisure time has been suggested to be valued from zero to average overtime earnings. Another approach is to value informal care at the market price of a close substitute also known as the replacement cost method [49].

Another issue is how to value productivity changes, i.e. indirect costs, and there is still an ongoing debate on what valuation method should be used. Most commonly the human capital approach is used, which estimates the value of lost production based on gross earnings for those employed [45]. It has, however, been argued that the human capital approach overestimates the cost of lost productivity due to illness since it does not take into consideration that sooner or later, the indisposed worker will be replaced and the productivity loss will diminish. For this reason the friction cost method has been suggested as an alternative to the human capital method. According to the friction cost method, only the disease-related production should be valued, i.e. costs which accrue until the initial production level has been restored [50]. One common critique to the friction method is that the approach is based on assumptions which are not in line with economic theory [51]. Recent researchers have suggested still another approach, where the value of a work absence may affect the team production and thus give a higher production loss than one [52].

Economic evaluation in health care

Economic evaluations can be defined as “the comparative analysis of alternative courses of actions in terms of both their costs and consequences” [45]. A health economic evaluation is always a comparison between two treatment alternatives or more within a defined patient group. It generates information that can be used by health care providers in their decisions on how to allocate resources.

Types of economic evaluation

Economic evaluation in health care is usually divided into four categories; *cost-minimisation*, *cost-utility*, *cost-effectiveness* and *cost-benefit analysis* [45, 53]. All four methods measure costs similarly, but they are distinguished by their different approaches on how to measure the consequences of the compared alternatives [45].

Cost-minimisation analysis compares treatments solely on the basis of costs. The method is used when there is reason to assume that the outcome of the therapies can be considered equivalent. According to this method, if two health care-programmes have equal outcome the least costly alternative is to be preferred [45].

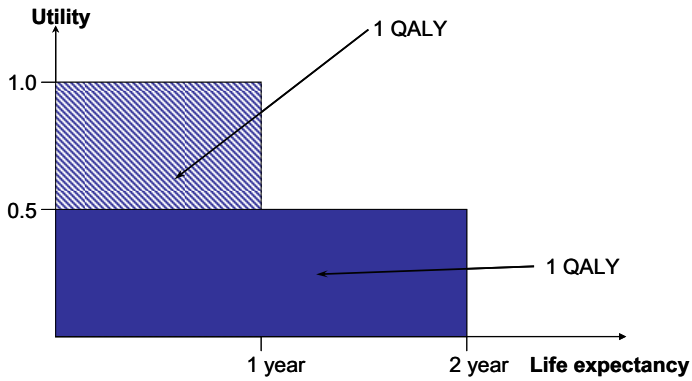
Cost-effectiveness analysis on the other hand assesses both treatment costs and outcomes. Effects (treatment outcomes) are measured in one-dimensional units, such as life years gained. The *Incremental Cost-Effectiveness Ratio* (ICER) is obtained by taking the ratio of the incremental difference in total cost (ΔC) to the incremental difference in benefits (ΔE) between programmes [45].

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_A - C_B}{E_A - E_B} \quad (1)$$

The ICER can be interpreted as the incremental cost of producing health effects by a treatment alternative compared to the next most effective alternative, and can be expressed e.g. as the cost per life year gained. This incremental ratio, as opposed to the average cost-effectiveness ratio, is the relevant variable to consider when deciding on the allocation of resources which maximises the health effects for a given amount of resources [51].

Cost-utility analysis (CUA) uses a generic outcome measure incorporating multi-dimensional consequences. As the outcome measure is not disease-specific, the relative merit of many different types of health care programmes can be compared across disease areas [44]. One frequently used measure is quality-adjusted life years (QALYs); a utility index that combines the consequences of survival and quality of life into one single measure [54]. QALYs are calculated by multiplying the number of life years gained by a utility value for the level of health status. The utility value ranges between 0 (dead) and 1 (full health), see Figure 5. The main methods used to measure utility values are time trade-off measurements, standard gamble or rating scale methods [54]. The most commonly used rating scale is the EuroQol five dimensions (EQ-5D).

Figure 5 Quality-adjusted life years

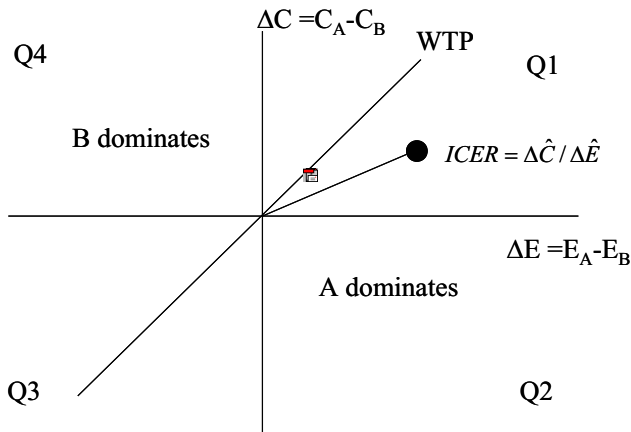


In *cost-benefit analysis*, both costs and outcomes are calculated in monetary terms. Benefits are best measured by the maximum willingness to pay (WTP). WTP are subjective valuations of the monetary value of health outcomes, measured by different techniques such as contingent valuation questions. If the value of the total calculated benefits produced by a programme exceed the value of the total costs, it is considered good value for money [44].

Interpretation of cost-effectiveness results

When two different mutually exclusive alternatives (i.e. the patient can only receive one of the treatment alternatives), for example treatment A and treatment B, are compared with regard to costs and effects, four different groups of results can appear, which can be illustrated in a so-called cost-effectiveness plane (Figure 6).

Figure 6 Cost-effectiveness plane



Source: Adapted from Drummond et al [45]

If A has a higher effect than B, at an equal or a lower cost (quadrant Q2), A is said to dominate B, and A should be preferred. If A costs more and has the same or a lower effect (Q4), then B dominates A, and B should be preferred. If, however, A costs less at a lower effect or costs more at higher effect (Q1 and Q3), the ICER must be valued by the decision maker. The optimal choice will depend on the willingness to pay (WTP) for an additional unit of effect.² If the maximum WTP can be defined, treatment A should be preferred to programme B if the ICER is below this threshold value [54]. In the figure, the WTP is illustrated as diagonal line that crosses origo. The WTP is the same for any given gradient, i.e. it is the same all along the line. If the ICER falls below the WTP line (e.g. the black point in Q1) treatment A should be chosen, while if it falls above the WTP, treatment B should be chosen.

Resource allocation to health care

Economic evaluation is a set of analytic tools to assess the value for money of alternative ways of allocating limited resources to health care. Formally defined, it is the comparative analysis of alternative courses of action in terms of both their costs and consequences [45]. Aspects of this definition need to be emphasized. The first is that economic evaluation is comparative, in other words it is only possible to comment on the value for money of a programme or intervention in comparison to another. The second point to note is that economic evaluation is focused on both resource effects (costs) and non-resource consequences, which include every impact that is potentially of value to users and potential users (e.g. health effects, convenience, access etc).

When can a health care programme be considered worthwhile to pursue? If the programme has lower costs and a better effect as compared to the comparator, the decision of implementation is clear. However, when the better effect is achieved at the price of an extra cost the decision is based on the valuation principle of the additional effect.

There exist two different principles on how resources could be allocated based on economic evaluations. The first is called the fixed budget approach. If the budget and the cost effectiveness for the relevant health care interventions are known it is possible to calculate the best allocation of the different interventions in order to maximise the effect. The second approach is to base the decision on a willingness to pay (WTP) for a gained unit of effectiveness (e.g. the value of a gained QALY). Currently there exists no definite threshold value set for a QALY. One suggested societal value of a QALY was estimated at SEK 655 000 in Sweden based on the value of a statistical life [55]. Another way of inferring threshold values could be based on past reimbursement decisions and guidelines made by national government agencies, such as those in the UK (\$32 000 – \$48 000/QALY) [56]. The WHO Commission on Macroeconomics and Health has suggested that interventions with a cost-effectiveness ratio lower than three times the gross domestic product (GDP) per capita for each averted disability adjusted life year (DALY) could be considered good value for money [57] in developing countries.

² A fixed budget rule can also serve as the decision rule [4].

Modelling

Modelling is used in many disciplines where information is provided as a basis for decisions under uncertainty. Fundamentally, modelling serves three basic purposes in health economics: (1) to simplify a complex reality by isolating aspects critical for the study (2) to combine data from different sources (e.g. economic data, clinical data, epidemiology data) and (3) to simulate consequences from alternative actions beyond the time frame of the data available to say something about the long-term consequences.

There are two main approaches that can be taken when performing an economic analysis. *The within trial analysis* or patient-level analysis is carried out alongside a randomised clinical trial. Resource use and effects are collected simultaneously with the clinical trial. The time frame of a within trial analysis is the same as the length of the clinical trial. However, the consequences of a treatment often stretch longer than the intervention period. In health economic evaluation all relevant costs and effects should be considered, regardless of when in time these occur. Moreover, clinical trial populations are often not fully representative of the target treatment population in clinical practice. To overcome these challenges, *decision-analytic simulation* modelling can be used when estimating the cost-effectiveness of a treatment. Simulation modelling integrates epidemiological, clinical and cost data from different sources and over time, related to the evaluated treatment strategies [45, 58]. A model is a simplification of the reality with the aim of excluding irrelevant details while maintaining interesting information relevant for the programme under study. The most common modelling techniques are decision-tree models, Markov cohort models and individual based simulation models.

In a *decision-tree model*, the expected probabilities and payoffs (i.e. costs and health outcomes) are calculated and compared between treatment alternatives. Decision-tree models are most appropriate for short-term analyses, or other situations when the number of possible outcomes is limited (e.g. acute illness).

Markov models are a specific type of discrete state-transition simulation models. A simulated cohort of patients is divided into a finite number of states based on, for example, the patient's current health status. One important assumption of the Markov model is the no memory assumption or the Markovian property, i.e. future events only depend on the current state of the patient, and not on prior events [59]. Markov models are especially appropriate to use when the disease under study is characterised by the recurrence of certain events and these are based on continuous risk over time [58]. Examples of such diseases are multiple sclerosis and depression.

Sometimes, it might be necessary to model changes in probabilities, costs and effects after an event over time. Because of the no memory assumption, this cannot be directly included in a health state in a Markov cohort model. In *Individual based simulation modelling*, patients are moved through the model one by one and not as a cohort. By letting each patient move through the model individually, it is possible to keep track of the model path history which can be used as information when probabilities, costs and effects are assigned through the simulation.

Discrete event simulation (DES) is a type of individual simulation modelling tool that has recently been introduced in health economics. DES is more focused on events than on a number of defined health states, as in Markov cohort simulation. Patients are followed over time and events occur at discrete time points and based on a list (called the event queue) keeping track of when the events occur. The main advantage with DES is that a patient can be in several activities at the same time which can be compared to a Markov cohort model where a health state must be defined for each possible combination of activities. DES has been suggested to be especially appropriate for diseases where the time to an event is a key factor in the epidemiology, for example cancer [45]. The drawback of DES is that it is heavily data intensive.

Uncertainty

Information from different sources are synthesized in cost-effectiveness models. The aim is to build and populate models with the most appropriate data and methods available. Despite these efforts, there is always an uncertainty in the estimated results in a cost-effectiveness analysis. The uncertainty in model based cost-effectiveness analyses can be classified into four different categories: methodological, modelling uncertainty, transferability/generalizability and parameter uncertainty [60]. Methodological uncertainty is the uncertainty arising when comparing study results that are based on different methods. This type of uncertainty has been suggested to be handled by sensitivity analysis and agreement upon a reference case model. Modelling uncertainty relates to the structure and process of the model developed, and may be handled by performing sensitivity analysis and reprogramming of the model. Transferability/generalizability uncertainty arises when the results from an analysis are applied to another setting. The uncertainty that has been given most attention in decision analytic modelling is the parameter uncertainty, which is the uncertainty relating to limitations in the underlying data in the model. One way of exploring parameter uncertainty is to verify its impact on the results from the cost-effectiveness analysis, i.e. sensitivity analysis. Another way of exploring the uncertainty is through probabilistic analysis, where the uncertainty in the relevant underlying parameters is taken into account by allowing some, or preferably all of them, to vary over a given range with a given distribution.

AIMS OF THE THESIS

The aims of the present thesis were to study aspects of the health economics of depression of importance for priority settings: the burden of depression to society, cost and health-related quality of life associated with patients treated for depression and modelling the cost-effectiveness of treatments for depression. The specific aims of the thesis were the following:

Economic burden of depression (paper I)

- To develop a model to estimate the economic burden of depression in Europe
- Produce the best possible estimate of the economic burden for each country and discuss explanations and consequences of the variations

Cost and quality of life in patients treated for depression (paper II-IV)

- To assess the societal costs for patients with depression at different stages of the disease and its treatment in Sweden
- To assess quality-of-life in patients treated for depression over the course of a depression episode
- To assess the association between achieving treatment goal and costs and quality-of-life

Assessing the cost-effectiveness of new treatments for depression (paper V)

- To develop a model to assess the cost-effectiveness of treatment for depression
- Assess the cost-effectiveness of a potential new treatment as compared to standard care

REVIEW OF LITERATURE

To get an overview of the history and development of health economic studies of depression, a literature review of previous research within the area was performed. The review was divided into studies of the cost of depression, quality of life, and cost-effectiveness of treatments for depression. Relevant studies were identified from the Health Economic Evaluation Database (HEED) and the MedLine database. All costs are presented in Swedish kronor and in year 2005 prices.

Cost of illness studies

The search for literature on cost of depression resulted in nineteen studies (Table 1). Seven studies were conducted in the UK, four in the US, four in Sweden, one in Germany and there were three multinational studies. Nine studies employed the top-down approach and hence, estimated the cost of depression at national/international levels. The rest of the studies reviewed used the bottom-up approach and thus, were based on a selected study population.

All cost of illness studies employing the top-down approach were based on registries and assumptions on health care resource use attributable to depression, and all studies except one estimated the cost to society. Andlin-Sobocki et al estimated the cost of brain disorders in Europe, based on epidemiology and cost data. The authors estimated the cost of depression at SEK 1 015 billion (€108 billion in year 2004 prices) [61]. Norinder et al estimated the cost of depression in Sweden at SEK 10.4 billion [21], and an older estimate reached SEK 20.2 billion (SEK 17.7 billion in year 1996 prices) [62]. Henriksson & Jönsson estimated the direct health care cost of depression at SEK 2.1 billion (SEK 1.8 billion in year 1996 prices) [63]. In the UK, Kind et al conducted a top-down cost of illness study and estimated the total cost of depression at SEK 60 billion (£3 billion in year 1990 prices) [64], whereas Thomas et al reached a cost estimate of SEK 131 billion (£9 billion in year 2000 prices) [17]. Jönsson & Bebbington estimated the health care cost of depression in the UK at SEK 4.4 billion (£222 million in year 1990 prices) [65]. The main differences between the UK studies can be found in different study designs and the methodology applied.

Greenberg et al conducted a cost of illness study in the US in the early 1990s, and estimated the total societal cost of depression at SEK 486 billion (\$44 billion in year 1990 prices) [66], which was updated ten years later and reached a cost of SEK 688 billion (\$83 billion in year 2000 prices) [67]. Reasons for the difference between the two estimates can be found in the improved methodology over time as well as the inflation between the two time periods.

Seven cost of illness studies were found in the literature employing the bottom-up approach, the majority of which only estimated direct health care spending on depression. Five studies were based on study populations from the primary care setting, whereas the others were conducted in inpatient care settings.

Chisholm et al conducted a multinational observational study in five countries (Australia, Brazil, Israel, Russia, Spain and the US), comparing the cost of health care for depressed patients [68]. The data collection was cross-sectional and resource-use was collected retrospectively (three months recall period). The average cost per patient varied greatly across countries, from SEK 270 per year in Russia (\$33 in year 2000 prices) to SEK 41 300 in the US (\$5 000 in year 2000 prices). The authors also reported work disability but did not value the productivity loss due to depression. The UK study by Creed et al [69] was a prospective follow-up case-control study of quality-of-life and direct medical resource use for five months following hospitalisation at acute medical wards in a large teaching hospital in Manchester, UK. The authors estimated an average cost of SEK 60 900-71 300 per patient over five months (\$7 600-\$8 900 in year 2000 prices). Peveler et al conducted a randomized controlled trial in the UK primary care setting, assigning patients different kinds of antidepressant treatment (SSRI, TCA and lofepramine) [36], and followed the patients for one year. The average cost was estimated at SEK 11 300 per patient and year (£834 in year 2005 prices). McCrone et al are the only ones who have investigated the cost of depressed children [70]. The study was conducted on a study population of 140 children in a UK primary care setting, and found an annual service cost of SEK 13 700. Knapp et al conducted a long-term follow-up study of adults who as children had been suffering from depression [71], and reported annual lifetime costs of patients with and without comorbidities.

Salize et al conducted an observational study in severely depressed patients attending psychiatric clinics in Germany [72]. Patients were followed for one year and health care resource use was recorded, leading to an average cost of SEK 21 700 per patient (€2 073 in year 1996 prices). Simon et al have conducted two different studies in the US, investigating the resource use and cost of depressed patients in HMO settings. Based on patient records and insurance records, they estimated the average cost per patient at SEK 22 600-40 600 (\$2 400-\$4 300 in year 1994 prices) [73], reaching similar results in an observational study in Seattle published in 2000 [22]. The most recent cost of illness study found in the literature is a randomized clinical trial of depressed patients treated in a Swedish primary care setting [23]. Von Knorring et al followed patients over two years and estimated a total cost of SEK 378 400 per patient (SEK 363 000 in year 2002 prices), of which indirect costs constituted 87%.

To conclude, a range of cost of illness studies are available in the literature. However, most studies are old and the cost of illness methodology has developed over the last decade. The design and aim of the selected studies as well as the methodology applied are different, which makes direct comparisons of the results obtained difficult. The studies reviewed clearly indicate that the cost of depression found outside the health care sector constitutes the bulk of the cost. Among studies employing the bottom-up approach, few have included costs from the societal perspective.

Table 1 Literature review of cost studies on depression

Author, year	Country	Study design	Perspective	Sample	Time frame	Cost	
						Total	Indirect
<i>Top-down approach</i>							
Andlin-Soboeki et al, 2005 [61]	Europe	Model	Society	-	1 year	1 015	730
Bolin & Jacobsson, 2001 [62]	Sweden	Registry	Society	-	1 year	20.2	16.2
Greenberg et al, 1993 [66]	US	Registry	Society	-	1 year	486	348
Greenberg et al, 2003 [67]	US	Registry	Society	-	1 year	688	472
Henriksson et al, 2004 [63]	Sweden	Registry	Society	-	1 year	2.1	2.1
Jonsson & Bebbington, 1994 [65]	UK	Registry	Health care	-	1 year	4.4	4.4
Kind & Sorensen, 1993 [64]	UK	Registry	Society	-	1 year	60	52
Norinder et al, 2000 [21]	Sweden	Registry	Society	-	1 year	11.7	9.3
Thomas & Morris, 2003 [17]	UK	Registry	Society	-	1 year	130.8	125.4
<i>Bottom-up approach</i>							
Chisholm et al, 2003 [68]	Multinational	Observational study	Health care	4 662	3 months	273-41326	-
Creed et al, 2002 [69]	UK	Observational study	Health care/service costs	263	5 months	60 906-71 324	-
Knapp et al, 2002 [71]	UK	Patient records	Health care/services	140	Lifetime	7 100 -16 700	7 100 -16 700
McCrone et al, 2005 [70]	UK	Patient records	Health care	140	1 year	13 700	13 700

Author, year	Country	Study design	Perspective	Sample	Time frame	Cost		
						Total	Direct	Indirect
Peveler et al, 2005 [36]	UK	RCT	Health care	324	1 year	11 321	11 321	-
Salize et al, 2004 [72]	Germany	Observational study	Health care	270	1 year	21 718	21 718	-
Simon et al, 1995 [73]	US	Patient records	Health care	6 257	1 year	22 643-40 550	22 643-40 550	-
Simon et al, 2000 [22]	US	RCT	Health care	290	1 year	20 771-38 946	20 771-38 946	-
Soboeki et al, 2006 [74]	Sweden	Observational study	Society	447	6 months	51 100	17 800	33 300
Von Knorring et al, 2006 [23]	Sweden	RCT	Society	1 031	2 year	378 361	50 031	328 330

Quality of life studies

When using QALYs as the outcome measure in a health economic evaluation, it is important that the quality of life is assessed using an instrument in line with utility theory. One example of an appropriate method is the standard gamble methods. The utility can be directly estimated using one of these methods or using generic instruments such as the EQ-5D which is based on 243 health states that have been ascribed utility values using the time-trade off method based on a general population sample [75, 76]. Another generic instrument based on a standard gamble method is the Health Utility Index (HUI)[77].

In cost-utility analyses of treatments for depression, it is necessary to have estimates on the utility for different health states of the disorder (most notably during a depressive episode). Having these, it is possible to calculate the area under the curve and estimate the number of QALYs over a given timeframe.

The literature review was restricted to published studies that estimated the quality of life using the EuroQol-5D (EQ-5D) instrument. The EQ-5D is the most commonly used instrument to assess quality of life and is in line with utility theory. Six studies were identified from the review (Table 2). Three of these studies were conducted in the UK, one in France and one in Sweden, respectively, and one was conducted in multiple countries in Europe. Only one of the six studies identified was a naturalistic observational study, and the rest were randomized controlled trials. Based on the selected studies, the average EQ-5D index score of an untreated depression episode ranges between 0.33-0.70 and improves by between 0.16-0.45, depending on the treatment given and the follow-up time. One explanation to the variation in the mean utility scores from the different studies may lie in the difference in study populations (most notably in the severity of the depression).

Peveler et al performed a randomized controlled trial in the primary care setting in the UK [36]. Patients were randomized to SSRI and TCA treatments and EQ-5D was assessed as a secondary outcome over twelve months. At baseline, the average EQ-5D index score was 0.59, and improved to 0.78 at the end of the follow-up, which corresponds to an improvement of more than 30%. Kendrick et al and Swan et al have also assessed the quality of life in depressed subjects in the UK [36, 78]. Kendrick et al conducted a randomized trial comparing usual care by general practitioners with enhanced patient management training in community nurses. The study was conducted in a primary care setting and reported a baseline EQ-5D index score of 0.63-0.70. The patients reported an improvement in quality of life of 0.81-0.85 over a follow-up period of 24 weeks. Swan et al studied the efficacy of a group-educational intervention in chronically depressed patients, and assessed the EQ-5D score alongside the trial [78].

A French observational study reported an even greater improvement in quality of life over eight weeks in patients treated for depression in primary care (EQ-5D index scores at 0.72-0.85) [79]. The study sample was, however, more severe, which might be the reason for the lower baseline average EQ-5D index value of 0.33. Sapin et al also showed an increased quality of life for mildly depressed people, as compared to more severe cases. A recently published randomized controlled trial conducted in Sweden assessed the effectiveness of improved disease management on treatment adherence

over a timeframe of two years [23]. EQ-5D was also assessed and a baseline average utility value of 0.61 was obtained. At a two-years follow-up the average EQ-5D index score increased to 0.77. Patients with an improved MADRS score of more than 50% scored somewhat better on the EQ-5D questionnaire as compared to those not responding as much to treatment.

Table 2 Literature review of quality of life studies using the EQ-5D instrument

Author, year	Country	Setting	Sample	Utility weights			
				Baseline	Follow-up	Response/non-response	Mild/Moderate/Severe
Fernandez et al, 2005 [15]	Europe	CUA (8 w)	126	0.52-0.54	0.77-0.78	-	-
Kendrick et al, 2005 [36]	UK	RCT (26 w)	246	0.63-0.70	0.81-0.85	-	-
Peveler et al, 2005 [36]	UK	RCT (1 y)	327	0.59	0.78	-	-
Sapin et al, 2004 [79]	France	OS (8 w)	250	0.33	0.78	0.72-0.85/ 0.58	0.74/0.44/0.30
Sobocki et al, 2006 [74]	Sweden	OS (6 m)	447	0.47	0.69	0.81/0.56	0.70/0.46/0.27
Swan et al, 2004 [78]	UK	RCT (24 w)	76	0.49	0.68	-	-
Von Knorring et al, 2006 [23]	Sweden	RCT (2 y)	1031	0.61	0.77	0.81/0.70	-

CUA: cost-utility analysis; RCT: randomized controlled trial; OS: observational study

To conclude, there are relatively few studies assessing the quality of life in patients with depression using the EuroQol (EQ-5D) instrument, especially over longer periods of time. Moreover, most of the studies were randomized controlled trials and thus, assessed quality of life in a highly selected patient population, in specific settings and under selected treatment conditions and strategies. Hence, there is a need for further research on the quality of life in depressed patients, as it is an important piece of information when conducting economic evaluations in the field.

Economic evaluations of treatments for depression

High levels of public spending, rising costs of treatments and scarcity of mental health resources have intensified the need for information on the cost-effectiveness of interventions for depression. The history of the economic evaluation of therapies for depression is largely driven by the introduction of new interventions. Broadly speaking, the first cost-effectiveness studies were published in the early 1990's and increased significantly with the introduction of SSRIs. In the last ten years, an increasing number of studies were conducted including non-pharmacological interventions, such as psychotherapy, counselling and patient care models, and then primarily studies in health management organization settings in the US.

The review of cost-effectiveness was restricted to published cost-effectiveness studies available on MedLine. Moreover, only studies using the QALY outcome measure were selected. By only including studies using a generic outcome measure like the QALY, comparisons between interventions and disease areas are made possible. Other outcome measures commonly used in economic evaluations of treatments for depression are; symptom-free days, remission and relapse avoided, and are often defined in slightly different ways. Almost 75% of the economic evaluations found in the literature use these alternative outcome measures.

In all, 22 cost-utility studies were identified (out of a total of 60 cost-effectiveness studies). The studies were categorised into four types of interventions: pharmacotherapy, psychotherapy, other interventions (e.g. counselling, collaborative models, training and education) and screening (Table 3). Ten studies were conducted in the US, nine in the UK and three in Canada. There was a mix of cost-utility analysis based on modelling and those where calculations were directly based on randomized clinical trials.

The majority of cost-utility studies evaluating pharmacotherapies was published in the 1990s and appraised the cost-effectiveness of selective serotonin reuptake inhibitors (SSRIs). However, a systematic review and model of the relative cost-effectiveness of SSRIs and TCAs in Canada reported that no antidepressant demonstrated a cost-effective advantage [80]. All cost-utility studies were based on models, except the most recent study published by Peveler et al, which is a randomized controlled trial with a follow-up of one year [36].

There is a growing body of literature indicating that psychotherapy is cost-effective in combination with usual care. However, published evidence suggests that it depends on the treatment setting and the depression severity of patients treated. Scott and Freeman evaluated cognitive behavioural therapy (CBT), but did not find any evidence for advantages in terms of cost-effectiveness as compared to counselling or pharmacotherapy [81]. Guthrie et al found interpersonal psychotherapy to be cost-effective in a secondary care-based study conducted in the UK [82]. Only one cost-utility study was identified in the literature, evaluating the relative and combined cost-effectiveness of IPT and antidepressants [83]. In the same study, Kamlet et al found maintenance treatment with imipramine alone to be the most cost-effective treatment strategy. Hence, present evidence indicates the need for further studies on the cost-effectiveness of psychological interventions.

A number of studies are conducted in the US and the UK, evaluating changes to the set-up and organization of the management of depressed patients [84-90]. These initiatives include patient education, support and progress evaluation as well as collaboration between physicians and other professionals. The selected studies in the present work indicate that the introduction of these new patient management strategies tends to generate better outcomes among patients, but the impact on cost is unclear.

Routine screening is an often discussed measure in the prevention and treatment of depression, as early detection of the disorder may improve outcomes and prognoses leading to lower long-term costs. The only cost-utility study identified evaluating screening was a study by Valenstein et al [89, 91], which found that screening had advantages in terms of outcomes but which came at a high cost.

Recently, there has been much debate regarding the real cost effectiveness of new treatments for depression, and critical appraisals have been made as to how reliable cost-effectiveness analyses found in the literature really are [92]. The methodology applied, the design of the study and the ability of the analysis to incorporate the most relevant information are crucial for the reliability, validity and quality of the economic evaluations conducted on interventions for depression. As can be noted from the literature search conducted in the present work, there are, all in all, rather few studies which include all relevant costs for the analysis and base the analysis on sound real-life data. Moreover, in Table 3, only studies measuring outcome in a generic way (i.e. quality-adjusted life years) were selected, and the majority of cost-effectiveness studies are based on disease-specific outcomes (e.g. treatment success and symptom-free days) [93]. The knowledge of the real efficiency of treatments for depression, as well as health economic consequences for depressed patients, has been insufficiently investigated until today and thus further studies would help decision makers in future.

Table 3 Literature review of cost-utility studies

	Country	Intervention	Study design	Patient population	Cost perspective	Time horizon	Cost per QALY gained (SEK in 2005)
<i>Antidepressants</i>							
Anton & Revicki, 1995 [94]	Canada	Nefazodone vs fluoxetine vs imipramine	Model	Working population	Health care	Lifetime	Nefazodone was cost-saving
CCOHTA, 1997 [80]	Canada	SSRIs vs TCA	Model	Working population	Health care		No antidepressant showed cost-effective advantage
Fernandez et al, 2005 [15]	UK	Escitalopram vs venlafaxin	Model	Primary care	Health care	8 weeks	Escitalopram was cost-saving
Hatziandreu et al, 1994 [95]	UK	Sertraline vs TCA	Model	Female recurrent depressive	Health care	Lifetime	4 100
Revicki et al, 1995 [94]	Canada	Nefazodone, imipramine, fluoxetine	Model	Women with MDD	Health care	Lifetime	Nefazodone is cost saving
Revicki et al, 1997 [96]	US	Nefazodone, imipramine, fluoxetine	Model	Managed care setting	Health care	Lifetime	23 500-56 900
Peveler et al, 2005 [36]	UK	TCA, SSRI vs lofepramine	RCT	Primary care	Health care	1 year	SSRI was cost-effective
<i>Psychological therapy</i>							
Guthrie et al, 1999 [82]	UK	IPT, counselling and usual care	RCT	Primary care	Health care	6 months	IPT was cost-saving
Kamlet et al, 1995 [83]	US	IPT, imipramine, IPT+imipramine	Model	Primary care	Health care	Lifetime	Imipramine is cost-saving to placebo, imipramine+IPT < \$ 64 000 vs placebo
Kaltenhafer et al, 2002 [97]	UK	CBT vs usual care	Model	Secondary care	Health care	2 years	17 600 – 112 200
Lynch et al, 2005 [98]	US	CBT vs usual care	RCT	Teenagers at HMOs	Society	1 year	77 000

Country	Intervention	Study design	Patient population	Cost perspective	Time horizon	Cost per QALY gained (SEK in 2005)
UK	Problem-solving treatment vs usual care	RCT	Primary care	Health care	26 weeks	Problem-solving is cost-saving
UK	Counselling, CBT vs usual care	RCT	Primary care	Health care	16 weeks	Not cost-effective
Other interventions						
US	Electroconvulsive therapy vs antidepressant therapy	Model	Recurrent relapsing elderly in community dwelling setting	Health care	1 year	198 200
UK	Psychiatric nurse vs usual care	RCT	Primary care	Society	1 year	Nurse care was not cost-effective
US	Collaborative care vs usual care	RCT	Elderly at HMOs	Health care	2 years	21 100-40 300
UK	Post-natal support worker vs usual care	RCT	Postnatal women	Health care		no health benefit of additional home visits by community postnatal support workers
US	Enhanced care vs antidepressant	RCT	Primary care	Society	1 year	124 600
US	Enhanced care vs usual care	RCT	Primary care	Society	1 year	47 500
US	Enhanced care vs usual care	RCT	Primary care	Health care	2 years	79 500-118 400
US	Enhanced care vs usual care	RCT	HMOs	Society	2 years	82 200-315 900
Screening						
US	Screen vs no screening	Model	Primary care	Society	One-time screening to annual screening	272 600-1 636 800

MATERIALS AND METHODS

International estimate of the cost of depression (paper I)

Costing model

The model developed for the present study is a novel approach to assess the cost of illness for Europe. It combines three main sources of data: economic data, epidemiology data and international statistics. The model was used to predict results for countries where no input data was available in the literature based on mathematical algorithms for imputation.

The model serves four purposes:

- (1) Time transformation of economic data. The original economic data was inflated to the year 2004 with the help of consumer price index (inflation).
- (2) Adjustment for international comparison. The collected economic data was transformed to Euro adjusting for differences in purchasing power (€PPP) across countries in Europe.
- (3) Imputation of data. For countries in Europe where no cost data was available, the model simulated cost estimates based on the available country-specific input data. An average of the selected economic input data was calculated and formed the basis for imputation. The calculated average costs were imputed per individual cost category (i.e. inpatient care, drug cost, outpatient care, indirect costs due to sick leave and early retirement, and indirect costs due to mortality). Algorithms based on indexes from international statistics were employed to eliminate price level differences across Europe in the simulations.
- (4) Assessing the cost of illness in Europe. The cost data was aggregated to national levels with the help of prevalence data for each European country and the estimates for each country were added together to yield an aggregated estimate of the cost of depression in Europe.

As the prevalence data collected only covered the working population, a weighted estimate was made for the costs occurring in the younger (0-17) and older (65+) age groups with depression. The weighted estimates only concern the direct costs and were assumed to follow the age distribution of the drug sales statistics of antidepressants, as a proxy for treatment intensity of these population groups. Weights were based on statistics from the Swedish pharmacy sales statistics [101].

The model was tested for its validity in two ways: sensitivity analysis of critical assumptions made in the model (internal validity) and comparison of the estimated costs with previous findings in the literature (external validity).

Costing

A bottom-up prevalence-based costing approach was applied for estimating the total cost of depression in Europe. The societal perspective was taken in the inclusion of cost categories, and the following cost components were included: inpatient care, outpatient care, drug costs, and costs due to productivity loss (sick leave, early retirement and premature death). No studies have estimated direct non-medical costs due to depression. The human capital approach was used as a valuation principle for indirect costs [42, 102].

Materials

European data on costs and prevalence of depression was collected from the literature. Moreover, national statistics were collected from international institutions.

Epidemiology data was collected from electronic databases (MedLine and Web of Science) complemented by regional and national registries (e.g. ESEMeD, GSH-MHS and NEMESIS). The literature search strategy also included local sources where English abstracts were provided. Point prevalence data was collected for depression by country. Where no data was available, best possible estimates or extrapolated data was used. An international group of epidemiologists in affective disorders were included in the project, to ensure the appropriateness of the literature review and the selection of data. The results from the review can be found in previous publications [5, 103, 104].

The literature search for cost data was based on all available English language publications from Europe using Medline and HEED (Health Economic Evaluation Database). The results from the reviews are presented in previous articles [103, 105]. A complementary search added two more studies to the cost input database for the cost estimations [21, 36].

National and international statistics were collected from several data sources. Population statistics and national welfare statistics (e.g. gross domestic product, health care expenditure) were retrieved from the Eurostat database 2004 [106] and OECD Health database 2004 [107]. Cost data was inflated to year 2004 with the consumer price index [108], converted to Euro, and adjusted for purchasing power parity [109, 110]. Indexes were calculated based on national welfare statistics and price level indexes retrieved from the Eurostat [106].

Health Economics of Depression In Sweden study (papers II-IV)

Study design and data collection

The study “Health Economic Aspects of Depression in Sweden” (HEADIS) was initiated to increase the understanding of the health economics of depression and to be used for economic evaluations. The study was a prospective naturalistic observational study of Swedish primary care designed to interfere as little as possible with the normal course of clinical work. Patient recruitment and data collection were performed at outpatient clinical centres in five different regions in Sweden. Geographically, only the northern part of Sweden had no representation. Both primary care centres and clinics specialized in company and occupational medicine were included. The physicians were randomly selected from listings of GPs in Sweden and were approached by mail and by phone. The participating physicians were free to choose the type and course of treatment in accordance with their usual practice. The study did not include any restrictions concerning the use of other therapies concomitantly with the antidepressant medication, and no additional medical visits apart from those that would normally occur were required except for a final medical visit after about six months of follow-up. Patients aged above 18 with a diagnosis of depression who started a new or changed treatment with antidepressants were eligible for inclusion. The study was approved by the local ethics committees and written informed consent was obtained prior to inclusion. Data collection began in 2004 and continued until October 2005.

Data was collected by a questionnaire at baseline and at revisits up to a six-month period of follow-up. Data on clinical and patient characteristics was collected at baseline and data on medical resource use and quality of life was collected at both upon inclusion and at revisits during the follow-up period. Two questionnaires were used for gathering data. The first questionnaire was completed by the physician, mainly in the presence of the patient, and concerned use of pharmaceuticals, outpatient and inpatient care, sick leave, and retirement. The second questionnaire was completed by the patient directly after the visit and assessed the patient’s quality of life using the generic quality of life instrument EuroQoL-5D [111]. The medical resource data was collected retrospectively at the time of each visit, e.g. the number of other medical visits since the previous visit.

Disease severity was assessed upon inclusion using the Clinical Global Impression-Severity of Illness scale (CGI-S) [16], and treatment improvement was assessed with the Clinical Global Impression-Improvement scale (CGI-I) [16]. The CGI-S is a 7-point scale assessing the current severity of the depression. The CGI-I scale is a 7-point scale that assessing the patient’s improvement (as judged by the physician). The CGI instruments have been employed in similar previous studies [23, 79, 112].

Quality of life

Quality of life was assessed with the EurQol-5D instrument. In the absence of specific social tariffs for Sweden at the time of conducting this study, the EQ-5D index tariffs derived by Dolan et al were employed [76]. The Dolan regression model for calculating EQ-5D index scores from the instrument generated values on a cardinal scale from 0 to 1. However, it also generated negative values, but these were set to zero in the base case calculations [44, 113].

Resource utilization

Direct costs included those for hospital care, outpatient care, and pharmaceuticals. Data on hospital care was recorded in terms of number of bed-days at hospital ward. Outpatient care consisted of physician visits (including phone help), specialist visits, nurse visits, psychologist/therapeutic visits, counsellor visits and emergency visits. Drug use included antidepressants and other medications. The patient was recorded as a user of a drug if she/he had been prescribed the drug. Dosage and treatment period were also recorded, and it was assumed that the drug was taken throughout that specified time period. Indirect costs included costs due to sick leave days and early retirement. Patient-reported resource use and resources lost, i.e. indirect costs, were recorded for the time period since the last visit during the follow-up period of six months.

Costing

All direct costs were estimated by combining the resource use data collected with unit costs for Sweden obtained from reference price lists. Unit costs for drugs were derived from the current price list at the Swedish pharmaceutical reference book (www.fass.se) and the National Corporation of Swedish Pharmacies (www.apoteket.se). For drugs other than antidepressants, the average daily costs were applied, based on unit costs from the National Corporation of Swedish Pharmacies. The indirect costs were estimated based on the human capital approach [42]. The average monthly pre-tax salary, including social insurance contributions, for all people fully employed in the private sector in 2005, was used to value lost production. The average working hours (stratified by gender) were also derived in order to calculate the average hourly labour cost in Sweden. All costs are expressed in year 2005 prices.

Remission

Health economic consequences of achieving clinical remission, were investigated in paper IV. A patient was defined as remitted in our data material by having scored: improved or very much improved, on the CGI-Improvement scale [16], combined with a clinical judgment of remission by the physician.

Statistical analysis

As the costs- and quality of life data analysed in paper II-IV was not generally normally distributed, non-parametric tests were used for differences between groups of patients. Analyses were conducted by sub-groups (sociodemographic and clinical characteristics) and between baseline and follow-up time periods. If the data was not found to be normally distributed the non-parametric Kruskal-Wallis one-way analysis of variance test was employed [114] and if shown to be normally distributed, the regular t-test was used [114].

Costs and health-related utility were presented as mean scores. To illustrate the uncertainty in the average point scores, 95% confidence intervals were calculated employing the bias corrected accelerated (BCa) percentile bootstrapping method [115]. The BCa method corrects for the bias and skewness of the sampling distribution through adjustment of the percentiles that determining the endpoints of the confidence interval.

Linear regressions were used in studies II-III to examine the influence of sociodemographic and clinical characteristics on cost and utility estimates. In the analysis investigating the relationship between costs and explanatory variables the Box-Cox method [114] was used to find the best transformation of the cost data to fit a normal distribution. The transformed cost variable was then used as the dependent variable in a multivariate ordinary least square (OLS) regression model. The Breusch-Pagan test was used to test for heteroscedasticity [116] and, in its presence, White's corrected standard errors were applied [116]. Determinants of time for achieving full remission were analysed employing a survival analysis technique [117]. The survival data was modelled employing a parametric proportional hazards model [117], and was fitted to the Weibull distribution [117].

All statistical analyses were performed using STATA 8.0 for Windows (StataCorp., College Station, TX).

Description of study sample

A total of 447 patients with depression were enrolled at 56 primary care centres in Sweden. 21 patients dropped out from the study before the first visit and thus baseline information was available for 426 patients. Another 28 patients dropped out from the study during the first follow-up visit and hence complete information on resource use and costs were available for 398 patients. In the analysis of the quality-of-life data another four patients had an incomplete response on the EQ-5D instrument resulting in 394 completers.

The average age in the sample was 47 (SD 14.2) at the start of the follow-up, and 67% of the patients were women. The majority of the patients were employed, and had at least completed high school. 67% of the patients aged below 65 were working. The majority (77%) of the patients experienced their first episode of depression at the time of inclusion. 59% of the patients reported at least one type of co-morbidity. The majority of the co-morbidities were somatic diseases, in particular cardiovascular disease, and the most commonly reported psychiatric co-morbidities were addiction and

panic disorder. 8% of the patients in the sample reported that they underwent psychotherapy in combination with the pharmacological treatment, and 26% of these were treated with cognitive behavioural therapy, while the rest received psychodynamic therapy. Suicidal tendency was reported by 7% of the patients. The average disease severity score was 3.9 (on a scale from 0 to 7).

Modelling cost-effectiveness of treatments for depression (paper V)

Modelling approach

A Markov simulation model [59] was constructed to simulate the course of events for subjects treated for depression over time (six months to five years). Four possible health states were defined: well, remission, episode, and dead. Patients were individually simulated in the model and started out with a current depressive episode. The patient started the simulation at a given age and moved through the states of the model according to a set of transition probabilities that occurred at monthly cycles. Patients remitted from the initial episode with a certain probability and, once remitted, the patient can either relapse or remain remitted. After six months of remission the patient was considered to be free from depression (well), which was an assumption based on previous research [118]. Patients being well had a certain probability of recurring and hence returned to the health state episode. The model allowed for multiple episodes throughout the timeframe of the analysis. Costs and utilities were assigned for each Markov state in the model. The model was programmed in TreeAge Pro Suite 8.2 (TreeAge Software Inc., Williamstown, Massachusetts).

Modelling a hypothetical intervention

A hypothetical treatment was included as a comparative alternative in the cost-effectiveness analysis. As the base case scenario the new treatment was modelled with an assumed 50% relative improvement on the probability of remitting from the depressive episode. In base case, the cost of the new treatment was, moreover, set equal to that of standard care. Standard care was defined from treatments given in the naturalistic observational study HEADIS, reflecting the current treatment patterns in Swedish primary care.

Patient population and setting

The model was populated with a patient cohort included in the HEADIS study, including patients starting treatment for a depression episode in a Swedish primary care setting. The cohort had a mean age of 47 years (SD 14.3), 67% were women, and 67% were working (with an age below 65). A total of 24% of the patients were mildly depressed (assessed with the Clinical Global Impression Severity Scale (CGI-S)) (13), 61% were moderately depressed and 15% were severely depressed upon inclusion. 59% of the population had a physical or psychiatric co-morbidity.

Data

The data needed for modelling the cost-effectiveness of treatments for depression is divided into three categories: clinical data (e.g. effect of treatment), health economic data (i.e. costs and quality of life) and epidemiological data (i.e. risk of relapse/recurrence and mortality)

Clinical data

The model developed in the present study was based on clinical remission as the measure of effect, and the clinical effect of standard care for depression was derived from the HEADIS study. Transition probabilities were calculated for time elapsing to remission, based on a Weibull regression model. The Weibull distribution is suitable for modelling data with hazard rates that increase or decrease over time and allows for the estimation of the probability of an event in different time intervals after the starting point, e.g. the probability of achieving remission within four months after the start of the episode. These types of calculations are not possible with other non-parametric survival analysis methods (e.g. Kaplan-Meier functions).

Health economic data

In the present study, cost data was incorporated in the model adopting the societal perspective. The costs included were those for inpatient care, outpatient care and drugs. Moreover, costs due to sickness absence were included. Cost of care and productivity loss was estimated for the different health states of the model using data from the HEADIS study. Costs were calculated by combining the resource-use data and sickness absence information with current unit prices for Sweden. In the model, all future costs were discounted to present value at 3% annually (which is recommended by the Swedish Pharmaceutical Benefits Board) and were presented for the year 2005 in Swedish kronor (SEK) (US \$17.5; €19.3).

The intervention cost for the new hypothetical treatment was, in base case, set at the same level as for standard care. The price was, however, altered in sensitivity analysis.

Quality of life was measured with the EuroQoL (EQ-5D) health status questionnaire and was used to estimate quality-adjusted life years for the model. The data from the

HEADIS study was used to populate the model. Utility weights derived from the HEADIS material were attributed to the health states “Episode” and Remission” in the model. For the health state “Well” the mean utility score was taken from a recent quality of life study of the general population in Sweden by Burström et al [119].

Other data

The relative mortality risk is higher in depressed patients as compared to the general population. The suicide risk was estimated at 20.4 times higher in the depressed population as compared with the general population [120].

Data on the long-term consequences of the disease was collected from the literature, as the follow-up period of the HEADIS study was too short to provide this information. The risk of relapsing from a depressive episode is substantial. The risk of relapsing within six months was estimated at 15% according to Geddes et al [121]. Once the patient had remained symptom-free (i.e. the remission state in the model) for six months she was considered to be well (recovered). The risk of recurring was set to 0.20 per year [122]. However, the risk was assumed to increase with the number of previous episodes (hazard ratio 1.15), in consonance with findings by Kessing et al [123].

RESULTS

Economic burden of depression (paper I)

The total number of people affected with depression in Europe was estimated at 21 million in 2004 compared to the total population of 466 million in Europe. This estimate is, however, only based on the working population, since prevalence data is scarce for the younger and elderly. If we were to assume the same prevalence estimates for the full population of Europe the estimate would reach 29 million people. The prevalence estimates ranged from 3% to 10% across Europe [5, 61, 103]. The highest prevalence estimates were found in Norway, Austria, Germany and Iceland, and the lowest in Italy and Spain.

The cost per patient with depression differed significantly across Europe, ranging from SEK 10 700 to SEK 73 100³. The cost was highest in countries with a high national income and health care expenditure per capita. The aggregated cost of depression was estimated at SEK 1 077 billion in 2004 in Europe, and corresponds to 1% of the European national incomes. The majority of the cost is found in the working population (89%), followed by the elderly who accounted for 11% of the cost. The youngest age group (aged 0-17) only constituted a minor part of the costs, the majority of which were outpatient care costs.

Direct costs amounted to SEK 380 billion, corresponding to 35% of the total cost. Outpatient care is the dominating health care cost, reaching SEK 203 billion in 2004 (19% of the total cost and 53% of the health care cost). The cost of drugs is estimated at SEK 82 billion, or 8% of the total cost. Hospitalization cost totalled SEK 95 billion (9% of the total cost). The bulk of the cost of depression is due to lost workdays and lost production caused by premature death. The indirect cost was estimated at SEK 695 billion, accounting for 65% of the total cost. However, the absolute majority of the indirect cost was caused by morbidity (due to sick leave and early retirement), i.e. SEK 659 billion (61% of the total cost). The cost of lost productivity due to mortality amounted to SEK 36 billion.

The cost of depression is unevenly distributed across European countries in absolute terms. The average cost of depression in Europe was estimated at SEK 2 310 per inhabitant, and is higher in Western European countries as compared to the newly admitted EU countries.

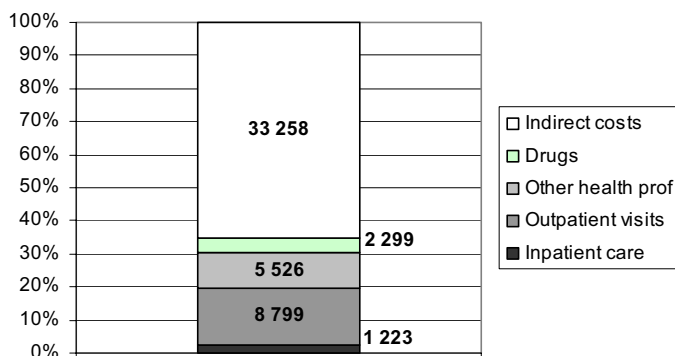
³ Based on an exchange rate of SEK 9.12 to Euro (Riksbanken)

Cost of depressed patients (paper II)

Patients with depression had, on average, seven outpatient visits during six months, and 0.3 hospital bed days. Physician visits were the most commonly reported type of outpatient visits. Depressed patients in the working force (aged 18-65) were, on average, absent from work for 68 days during six months (or 45 days based on the full study population), and 6% of the patients were in early retirement. Based on this data, the cost per patient was estimated at SEK 51 100 (95% CI: SEK 46 100-56 500) for six months (Figure 7). Medical care costs amounted to SEK 15 500, consisting of inpatient care (SEK 1 200), outpatient care (SEK 8 800) and visits to other health professionals (SEK 5 500). The costs of drugs were estimated at SEK 2 300, 91% of which were costs of antidepressants. Indirect costs amounted to SEK 33 300 (95% CI: SEK 28 700-38 200), accounting for 65% of the total costs. The second largest cost component was outpatient visits, which represented 17% of the total costs. Treatment with antidepressants constituted 4% of the total cost. In annualized terms the total cost per patient reached SEK 102 200 (95% CI: SEK 92 200-113 000).

The cost increased with depression severity ($p < 0.05$); SEK 45 500 for mild cases and SEK 49 700 and SEK 65 400 for moderate and severe cases, respectively. The total cost per patient in the working population (aged below 65) amounted to SEK 56 300, and there was no significant difference in total cost between age groups in the working population.

Figure 7 Distribution of total annualized cost per patient (SEK2005)



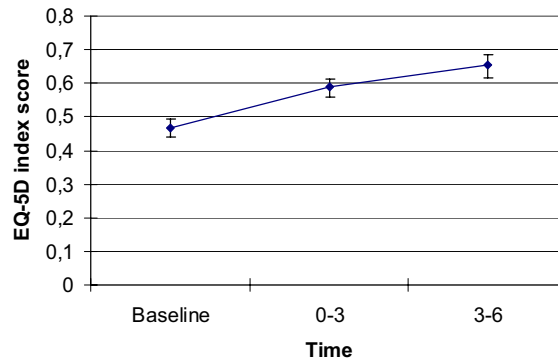
Regression analysis showed that demographic variables did not explain the differences in cost of depression. However, patients on sick leave due to their depression are associated with a significant increased cost, and patients who are treated to a symptom-free state are associated with a markedly decreased cost.

Quality of life in depressed patients (paper III)

Health-related quality of life was assessed with the EQ-5D (EuroQol) instrument. Upon inclusion, depressed patients have a health-related utility score of 0.47 (95% CI: 0.44-0.50), which is an impairment of 45% as compared to the general population. Depressed patients report negative impact on their daily activities, an increased level of pain and discomfort, as well as anxiety and depressed mood.

The patients reported a statistically significant increase in utility during the six-month period of treatment (Figure 8). The average utility score 0.69 (95% CI: 0.67-0.72) at the end of the study represented an increase of 0.23 as compared to the baseline (95% CI: 0.19-0.26).

Figure 8 Average EQ-5D index score during follow-up



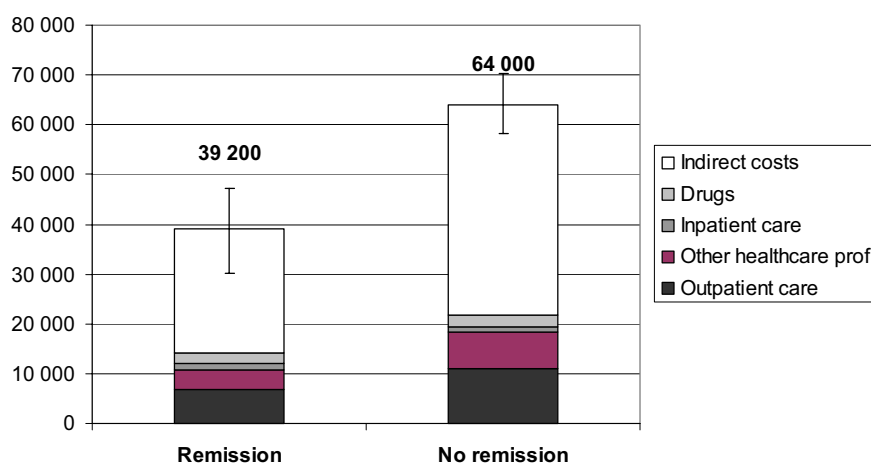
More severely depressed patients rated their quality of life significantly lower (0.27) as compared to moderately and mildly depressed patients (0.46 and 0.60 respectively), but irrespective of the severity of the depression, utility scores increased for all patients during the treatment period (0.62, 0.69 and 0.76 respectively). Patients who have combined pharmacological treatment with psychotherapy reported higher utility scores than patients only treated with antidepressants. Men and women reported rather similar EQ-5D index scores, but patients aged below 65 rated their quality of life lower than patients aged above 65. Patients with co-morbidities reported lower quality of life than those without.

The regression analysis showed that, all else equal, patients achieving clinical remission during the study period reported a 26% higher average utility. Moreover, patients on sick leave due to their depressive episode (at any time throughout the follow-up period) were associated with 6% lower utility. The results also showed that patients who reported a suicidal tendency were associated with lower utility. Treating patients to clinical remission was associated with an increased EQ-5D score of 39%.

Health economic consequences of achieving remission (paper IV)

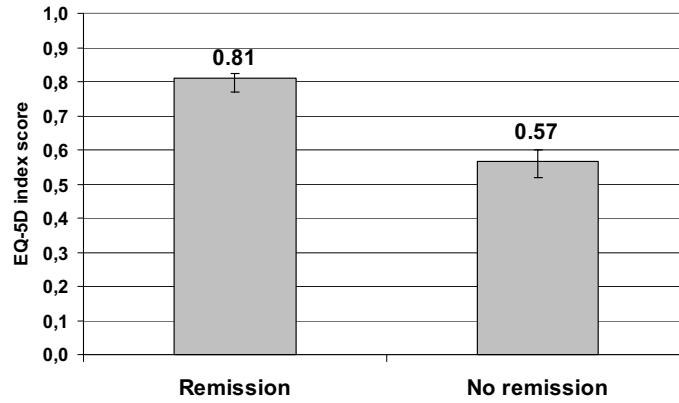
Patients who were successfully treated to full remission from their depressive symptoms had, on average, three outpatient visits less than non-remitting patients over a period of six months ($p < 0.01$), and were absent from work 22 days less ($p < 0.01$). This translated into a statistically significant cost reduction of SEK 24 800 or SEK 49 600 in annualized terms (Figure 9). For the working population the cost results reached SEK 43 600 and SEK 69 600, for remitting and non-remitting patients, respectively. There was only a marginal change in the results when adjusting for baseline characteristics between the response groups.

Figure 9 Total cost of depression by remission status (SEK 2005)



At baseline, remitting patients had a mean EQ-5D index score of 0.52 and non-remitting patients 0.40. At the end of the follow-up, the remitting patients reached an average EQ-5D index value of 0.81 (95% CI 0.77–0.83), corresponding to an increase of 0.28 ($p < 0.01$). Non-remitting patients increased their utility to 0.57 (95% CI 0.52–0.60), i.e. an increase of 0.16 ($p < 0.01$) as compared to baseline (Figure 10). The average difference in the utility score between remitting and non-remitting patients was estimated at 0.24 (95% CI 0.19–0.27) at the end of the follow-up; an improvement of 40% ($p < 0.01$). The difference was statistically significant ($p < 0.01$). Adjusting for differences in baseline characteristics only marginally changed the results.

Figure 10 Average EQ-5D index score at end of study by remission status



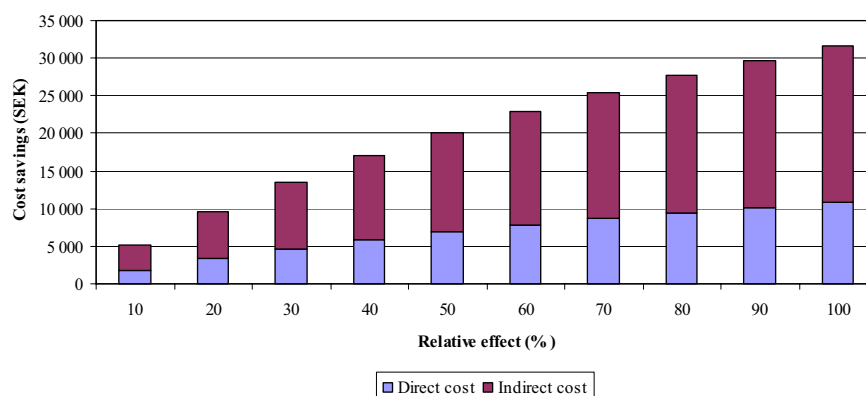
A total of 52% of the patients reached full remission at the end of the follow-up period. The median time to remission during a six-month follow-up was 135 days (SD 3.98). Patients with severe depression had a significantly lower chance of achieving remission during follow-up, as compared to mild and moderate cases ($p < 0.01$).

Assessing the cost-effectiveness of a potential new treatment (paper V)

Patients were simulated through the developed Markov model over a time frame of five years in base case. The patient cohort simulated was treated as usual (based on the treatment patterns in the HEADIS study) for acute depression episodes. Thus, all patients started the simulations in the health state “episode”. In consequence, with the transitions of patients over time, the costs were increasing most heavily during the first year after the index episode and the accumulated cost for the first year amounted to SEK 95 300. At five years, the accumulated cost was SEK 157 700. The total number of QALYs was 0.70 after one year, 1.46 after two years and 3.62 after five years.

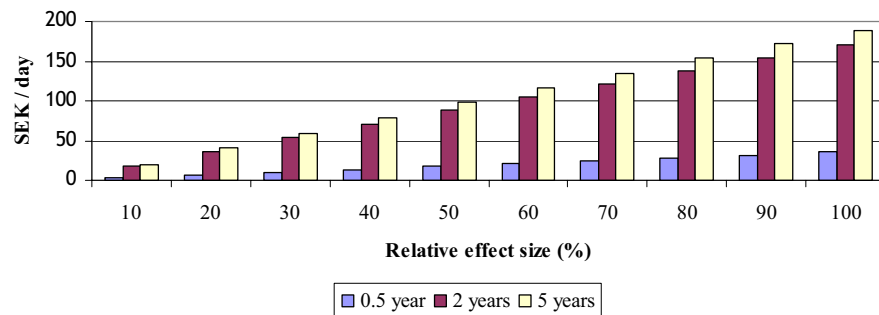
A new treatment was compared with standard care, with an assumed effect improvement of 50% on the remission rate. In base case, the cost of the new treatment was set equal to that of standard care. The new treatment produced statistically significant cost savings even for the shortest time frame (six months), or SEK 2 300 to SEK 20 100 for 6 months and five years respectively. There were both cost reductions in health care costs as well as indirect costs. With a five-year time frame, the total direct costs for patients with standard care resulted in SEK 52 900, as compared to SEK 46 000 for the intervention group. This corresponded to a difference of SEK 6 900. However, the main cost saving was made in indirect costs, where the intervention produced a cost reduction of SEK 13 200. The QALY gains were 0.011 to 0.073 QALYs for a six-month to a five-year time horizon. Varying the relative treatment effect size of the new treatment had dramatic impact on the potential cost savings (given the same cost of the intervention as for standard care), see Figure 11. The QALY gains varied from 0.002 to 0.12 QALYs depending on the relative effect of improvement on the remission rate and the time frame given.

Figure 11 Estimated cost savings for different relative effect sizes (five-year time frame)



By introducing a premium price for the hypothetical intervention, we could assess at what levels of treatment effect the new therapy was no longer cost saving. At a relative effect improvement of 50%, the premium price for the new intervention varied from SEK 17 per day to almost SEK 100, depending on the time frame. The intervention cost varied substantially with the level of effect (Figure 12).

Figure 12 Threshold intervention cost at different effect levels and timeframes (premium cost in SEK/day)



Sensitivity analysis showed that by also assigning the same relative treatment effect of 50% to the risk of relapses, the cost savings increased to SEK 23 700, and QALYs gained increased to 0.08 over a five-year time frame. Furthermore, by assuming the same effect on risk of recurrence, the cost savings reached SEK 36 400. Increasing the time frame for the analysis substantially increased the levels of cost saving. No cost of adverse effects was assumed due to the new intervention, but introducing such a cost only marginally changed the results. In base case, the new intervention was assumed to have no reduction in mortality risk as compared to standard care. Varying the absolute mortality risk levels and discount rates made little changes to the results.

DISCUSSION

The economic burden of depression and measures to reduce it

Paper I shows that depression is a prevalent disorder in Europe, which causes a substantial economic burden to the health care systems, as well as to wider society. A total of 21 million Europeans suffer from depression which causes an annual cost of almost SEK 1 100 billion (€118 billion), which corresponds to 1% of the European national income (GDP).

The study shows that the bulk of the costs of depression are so called indirect costs (65% of the total cost), i.e. due to productivity loss from morbidity and suicides. Moreover, outpatient care comprises more than half the health care costs for depression (53%), whereas inpatient care constitutes a smaller proportion than what is reported in older cost studies [64, 65, 124, 125]. This is not surprising taking into account the health care reforms carried out in Europe, shifting the care of depression from the inpatient to the outpatient settings. We expect our overall estimate of the cost of depression to be conservative. Production loss due to suicide is scarcely studied in the literature and often neglected in cost of illness studies on depression, but there is a literature suggesting that cost of suicide constitutes a greater share of the total cost of depression than what was presented in paper I [62]. Moreover, neither direct non-medical costs nor costs of informal care were taken into account in the estimates presented here. Further research on these cost items is needed.

Paper I did not include so-called intangible costs. These are costs associated with pain, psychosocial suffering, and changes in social functioning and activities of daily living caused by a disease. One way of measuring these costs is to compare patients' health-related quality of life (QoL) scores to those of an age and gender matched sample of the general population [126]. A widely used instrument to assess health-related QoL is the EQ-5D questionnaire [111]. We have shown that patients treated for their depression have a QALY of 0.7 over 1 year [74]. Assuming a matched utility score for the general population at 0.85, the annual QALY loss equals 0.15. Applying a value of a QALY at two times the GDP per capita for a country in Europe, the annual intangible cost of depression would reach SEK 1 700 billion. If we were to assume the same quality of life as measured at baseline in paper II for all depressed patients in Europe (EQ-5D index score of 0.47), the intangible cost would reach SEK 4 400 billion. This should be compared to the estimated direct cost of depression at SEK 400 billion and indirect costs at SEK 700 billion.

In paper I, indirect costs due to suicide were valued based on production loss. However, it has been argued that the valuation of mortality should both include production and consumption [127-129]. Taking this consideration into account, the cost of premature death due to suicide might be overestimated in paper I. The size of the cost will, however, depend on the age of the patient. Elderly patients (in retirement) consume

more resources than they produce, while younger people produce more than they consume. If we were to adjust the estimate of indirect costs due to mortality in depression with age-stratified data from Sweden on consumption and production [130], we would reach a reduction by more than 75%.

In Paper I, a new approach was developed to estimate the cost of illness internationally, introducing a way of imputing cost values from one country to another by adjusting for purchasing power differences between countries. In paper I we concluded that the model seems to generate reliable estimates of costs in Europe. There are, however, several concerns with extrapolation of epidemiology and cost data from one country to another. The data employed in the costing model was derived from a limited number of studies with various objectives, designs and methods. Although the cost estimates provided in Paper I seem to be reliable on an aggregated level, there is a considerable degree of uncertainty concerning the cost estimates for the individual countries included. Nevertheless, there were considerable differences seen in the cost of depression across countries in Europe, ranging from less than SEK 600 per capita in the Baltic countries to more than SEK 4 000 in some Western European countries (e.g. Germany and Norway). The proportion of indirect costs compared to the total cost of depression also varied substantially across countries, from 50%-80%. It is plausible that these differences are not solely due to the effectiveness of treatment and management of depression in individual countries, but also due to differences in the structure of welfare systems across Europe. In general it can be noted that the proportion of indirect costs is higher in countries with higher national incomes per capita.

How can we then relieve the heavy economic burden of depression? Evidence suggests that depression is still heavily under-diagnosed in society [73, 131]. Primary care is the most important health care provider detecting depression but despite its importance, there is a great need to optimize diagnostic and therapeutic procedures, as depression is often masked by somatic symptoms [132]. Recent American research confirms that there is a need to improve the management of depressed patients and suggests a more proactive case detection, patient activation (i.e. making the patient aware of her disorder), better clinical assessments and better collaboration with other mental health specialists [90, 133, 134]. Hence, better detection, prevention and management of depression are important components to reduce the burden of the disease for the afflicted and reduce its economic consequences to society. These factors need to be more carefully evaluated in the health care setting.

More than 90% of the countries in the world have no mental health policy, and health plans frequently do not cover mental disorders such as depression [2]. It can thus, be assumed that there is a great uncertainty of the actual burden of depression both in terms of undetected cases of depression and reluctance to treat due to economic restrictions for the individuals afflicted. Thus, there is a need for an increased attention to the disease in society in general, and to acknowledge the disease in the health care system. This is particularly important, since stigma is a common barrier to seeking help for depression [135].

Total funding for research on depressive disorders amounted to about SEK 5.6 billion in 2005 (€610 million) [74], of which public funding only accounted for 6%, and industry funding 94%. Hence, funding of research on depression only constitutes 0.6% of the total cost of the disorder. There have been a number of innovations in terms of medical

treatments for depression in the last decades, and the benefits seem substantial in relation to the investments made. Further funding for research on depressive disorders is therefore likely to be cost-effective [74].

Cost of depressed patients

In paper II, patients with depression were found to be associated with a substantial economic cost, in particular due to the reduced ability to work and disease-related absenteeism. Our results also indicate that the cost per patient increased by the severity of depression, and that treating depressed patients to remission is an important goal to reduce the cost of the disease.

In paper II, we found indirect costs to account for 65% of the total cost for a depressed patient (consisting of cost for lost production due to sick leave and early retirement), which is in line with the estimate achieved in the cost of illness study in paper I. Our findings are in good agreement with previous findings, with proportions ranging between 61-97% of the total cost of depression [17, 21, 64, 66-68, 136]. Costs due to suicide were not valued in the HEADIS study. However, it can be assumed that these costs are relatively small in the study population selected, as the study was carried out in a primary care setting. Health care costs were estimated at SEK 17 800 (SEK 35 700 in annualized terms), which is in line with a recent clinical trial [23]. The cost of outpatient care constituted half of the health care costs, which was the same proportion as found in paper I. It should, however, be noted that inpatient care is most likely underestimated in the HEADIS study, as patients were solely recruited in the primary care setting.

Relatively few cost studies have estimated the indirect costs of depression. Von Knorring et al conducted a bottom-up study and found substantially higher estimates for primary care patients in Sweden, as compared to the results presented in paper II [23]. If the annualized cost results from the HEADIS study (SEK 102 200) were to be extrapolated to a national level, given a point prevalence of 6.9% for depression (used in paper I), the cost of depression would reach SEK 64 billion, which is far more than what has been reported in cost of illness studies employing the top-down approach [21, 62, 63]. This is not surprising, however, due to the differences in the two costing methods. With the bottom-up approach, we can include a broader set of resources (e.g. visits to other health professionals than GPs and psychiatrists, and non-pharmacological treatments). It should, however, be noted that the HEADIS data is based on a study population which constituted “users” of health care, and was recruited during the acute phase of the depression. Hence, the study population in HEADIS might not be fully representative of the whole population of depressed people in Sweden. Nevertheless, previous research confirms there to be a difference between the two costing approaches. Studies on the cost of multiple sclerosis found a three-fold difference in the estimates based on the bottom-up approach as compared to the top-down approach [43, 137]. The corresponding relationship was 4:1 in diabetes [43]. Comparing the results from paper II (SEK 64 billion) with those of paper I (SEK 25 billion in 2005 prices), we found a relationship of 2.5:1 in depression.

The cost analysis based on the HEADIS study illustrates the methodological challenge in separating cost of care, due to a disease from cost of care of patients with a disease. Health care visits and treatments reported in the HEADIS study were both collected as due to depression as well as due to other causes (e.g. co-morbidities [138]). Since co-morbidities are common in depression, it is not always easy to know which costs are attributable to depression and which are due to other causes. This is especially critical for indirect costs in depression, as the reason for absenteeism may be due to a somatic disease rather than the depression, although the depression plays an important role for the patient's ability to work. We found a rather small difference in the cost due to depression and the cost of patients with depression (SEK 51 000 vs. SEK 56 000) in paper II. However, for the elderly study population, the direct health care costs were twice as high when including all costs for the patients as compared to costs related to depression. The presence of potentially interrelated co-morbidities means that it is questionable whether a distinction between total and disease-related costs is meaningful for a condition like depression, but more research is needed to provide a better insight into the matter. It seems particularly important to further investigate cost of depressed elderly.

Quality of life in depressed patients

Paper III shows that quality of life for people with a depressive episode, measured with the generic EQ-5D instrument, was almost 50% lower compared with the average person in the general population [19, 113]. In absolute terms we estimated the average utility score of a patient with a current episode of depression at 0.47, which is in range with what similar previous studies have reported (Table 2). This decreased level of quality of life is comparable with other serious health states, such as a moderate to severe stroke and heart disease [139, 140]. We have found that quality of life decreases with severity of depression, and these findings are in consonance with those in earlier research [79].

In paper III, a number of methodological aspects of the assessment of quality of life need further attention. First, it was unclear how well the generic EQ-5D instrument would measure quality of life in depression, as there are a limited number of previous studies using the instrument on depression. Paper III does, however, indicate that EQ-5D can assess important aspects of quality of life of the disease and that the instrument includes items relevant for the disorder (e.g. discomfort and pain from disease, impact on daily activity and related anxiety and mood changes). Further studies are, however, needed before any conclusions can be drawn on the validity of the EQ-5D instrument in measuring quality of life in depression. A second methodological issue that needs further attention is the method for calculating index scores based on the EQ-5D instrument. The development of the methods for calculating index scores is based on regression models [75, 76]. Based on results from regression models presented by Dolan et al, the utility weights theoretically range from -0.59 to 1. However, utility theory does not allow any interpretation of non-positive utility values; the lowest value is set to zero, representing the worst possible health state (death). In consequence with utility theory, non-positive values were set to zero in the base case calculations presented in paper III. From a pragmatic point of view, one could, however, argue for

health states worse than death, e.g. severe or suicidal patients with depression [79]. Additional utility calculations were conducted, allowing for non-positive values, but showed to have a marginal effect on the results. A third methodological aspect concerns the tariffs employed in the calculations of utility scores. In paper III, the tariffs provided by Dolan et al were used [76], as there exists no similar data for Sweden. However, there is ongoing research aiming at deriving tariffs for Sweden. The tariffs derived by Dolan et al are referred to as *social* tariffs, since they are based on health state valuations in a general population sample. The alternative would be to base the valuations on individuals who are in the actual health state (i.e. depressed patients). As no specific elicitation of the *individual* tariffs of depressed patients exists in the literature, no comparison of results employing this alternative approach could be made in paper III. There is an ongoing debate on which tariffs are most appropriate to use. However, the choice of tariff ultimately depends on the purpose of the use of the quality of life data and the view point of the reader [141]. If the utility data is used for calculations of QALYs in economic evaluations, some suggest that the social tariffs may overestimate gains in QALYs as compared to individual tariffs [119]. Further research on the assessment of quality of life in depression is desired to investigate the methodological issues mentioned above.

The mission is remission

The understanding has grown during the last decades in the psychiatric community, that many depressed patients only respond partially to treatment and that further efforts are needed from the treating physician to reach the optimal goal for the treatment: clinical remission [13]. However, in clinical trials effectiveness is, most commonly, measured as a 50% improvement (e.g. measured on rating scales such as HAM-D and MADRS). This is not equivalent to the definition of clinical remission where the patient should be free from the depressive symptoms, as this measure is relative, and hence depends on the patient's severity of depression.

The clinical importance of full remission is increasingly recognized in the literature [142, 143]. The consequences of not achieving full remission can be serious for the depressed patient, leading to greater risk of relapse/recurrence, more frequent depressive episodes and shorter periods between episodes [144-146]. It may also lead to increased mortality and morbidity [122, 147-157]. Treating patients with depression to a state of full remission (full symptom resolution) is associated with a significantly improved long-term outcome, including a reduced risk of relapse and improved psychosocial functioning [5, 144, 146, 158]. Residual symptoms are strong predictors of subsequent relapses. Paykel [5] has reported that after 15 months of follow-up, relapses occurred in 76% of the patients with and in only 25% of those without residual symptoms.

Remission is, however, a more problematic issue from an economical point of view, as more patients always will be able to reach remission at increased costs. The question from an economical point of view is, rather, to find the optimal balance of number of patients in remission to the cost of achieving this. It may be that we are currently under treating depressed patients, and thus the marginal costs of getting more patients into remission are small in relation to the benefits generated. This is why economic

evaluations are necessary and modelling which can predict the streams of costs and benefits from different treatment strategies for depression, and further such studies are needed before any judgements can be made on optimal treatment goals for depression.

In the present thesis, remission is shown to be a key health economic parameter. By treating depressed patients to remission, the patients' perceived quality of life increase by more than 50%. Moreover, patients who became symptom-free were associated with fewer health care visits and missed work days, as compared to patients who still remained depressed. Hence, the present thesis provides an indication that substantial costs can be gained by managing depressed patients to a symptom-free health state.

It is intuitive that treating depressed patients to remission might have positive impacts on both the costs and the quality of life. In the HEADIS study, it was, moreover, possible to establish how effective treatments for depression are in clinical practice. We observed that only half of the patients treated with antidepressants (and other therapies such as psychotherapy) reached a symptom-free state within a time-frame of six months, which is in agreement with findings made by previous researchers [159]. It was, moreover, seen that relatively few switches and augmentations of drug treatments were made over the treatment period. This strongly indicates that there is room for further improvements in the treatment and management of depressed patients in primary care, which strongly needs further research attention.

There are a couple of limiting aspects to the interpretation of the results of paper IV. It is difficult to make causal relations in non-controlled observational studies, but rather associations can be observed. Moreover, remission was only assessed with the help of a rather simple rating scale (CGI) and the treating physician's judgement. However, this was in line with the naturalistic design of the study and it is difficult to see how more rigorous instruments could be used in clinical practice in primary care without violating too much with the normal course of work. To improve the assessment of treatment goal in clinical practice, it could be suggested that the patient should perform a self-examination on her own [160].

Use of naturalistic studies in economic evaluations

Randomized clinical trials (RCT) have become the standard for establishing the efficacy and safety of new therapies. The design of randomized clinical trials (RCT) has the advantage of isolating the phenomenon under study by selecting a patient population of interest with strict inclusion and exclusion criteria. RCTs also provide high interpretability, statistical rigor, control of bias and are based on well-established and accepted methodology. Therefore, the internal validity of such studies is high.

RCTs are more frequently used directly to evaluate the cost-effectiveness of new interventions for depression (Table 3). Solely relying on RCTs may limit the external validity and generalization of the economic impact of a treatment in real world practice. Some commonly raised weaknesses of controlled RCTs are, that they may include questionable choices of comparator therapies (e.g. placebo), have inadequate sample sizes, limited duration of patient follow-up, inability to separate protocol-driven costs

from actual costs of care, and choice of outcome measures that may not be relevant to standard or usual care (e.g. relative response) [45]. These weaknesses are often observed in RCTs on interventions for depression and threaten the generalization of the results.

Alternative strategies to overcome the problems associated with cost-effectiveness studies based on RCTs could be to conduct RCTs naturalistically and/or to collect data in a separate observational study. Peveler et al conducted an economic evaluation based on a naturalistic RCT [36], where patients were followed for one year in clinical practice. The HEADIS study (paper II-IV) is an example of a naturalistic observational study collecting health economic information that is useful in economic evaluations (paper V). The advantage of naturalistic observational studies is that the data collected may be generalizable as patients are observed in clinical practice. Naturalistic observational studies, moreover, provide the possibility to study variations in clinical practice using different inference techniques (e.g. instrument variable, propensity scoring and difference-in-difference), which is of value for the understanding of how the management of patients could be improved. This is an area, which need further methodological development in future.

The HEADIS study has some weaknesses that should be considered when conducting future naturalistic observational studies on depression. First, due to financial and time constraints, patients from psychiatric clinics were not included. This would have increased the generalizability of the results, and would have included more severe cases of depression. Second, we intended to interfere as little as possible with the HEADIS study in the clinical practice. Therefore, simple instruments and non-rigorous rating scales were used to assess severity of depression and treatment improvement during the follow-up period (CGI-S and CGI-I). In retrospect, the specificity and generalizability of these assessments would have been improved adding more comprehensive instruments (e.g. MADRS), and increased the possibility to link the data to other data sources (e.g. clinical trials). Third, we restricted our collection of resource use data to health care use and information on working capacity (indirect costs). There is no previous cost study thoroughly investigating the direct non-medical resource use in depressed subjects (Table 1). Cost of informal care (e.g. care by family) was, furthermore, not included in the cost estimates. Evidence suggests that depression causes distress for families and other caregivers, resulting in potentially high costs for informal care [161, 162].

Modelling the cost-effectiveness of depression treatments

Computer simulation models are used to combine data from several sources, to make extrapolations and predictions beyond the data available, and to explore alternative scenarios when data or assumptions are uncertain (i.e. sensitivity analysis). Data from clinical trials are often used in economic evaluations. A disadvantage of clinical trials is that they often have short follow-up periods as their primary purposes are to establish the safety and efficacy of a treatment. Models can, hence, be used to extrapolate clinical trial results for a longer time period based on assumptions and other data sources (e.g. epidemiology data). Moreover, models can be used to translate the efficacy measure, reported in the clinical trial, to a more generalizable effectiveness measure (e.g. QALY).

Models also provide the possibility to explore the uncertainty in the data and assumptions used, and hence give an understanding of the overall uncertainty in the interpretation of the results from an economic evaluation. The disadvantage with modelling is that it is data intensive, and that the quality of the modelling results is highly dependent of the quality and appropriateness of the data used in the model. Moreover, models can be perceived as complicated and non-intuitive.

About half of the cost-utility analyses conducted on treatments for depression are based on modelling (Table 3). However, only a few of all previously published cost-effectiveness analyses of treatments for depression comply fully with the methodology recommended in health economics [45]. Few studies include costs from the societal perspective, and most studies were not based on the preferred effectiveness measure, QALY [93]. Moreover, most previous cost-effectiveness studies are based on clinical data measuring treatment response as opposed to clinical remission. Paper V provides a new model to evaluate treatments for depression trying to incorporate the fallacies identified in previous economic evaluations. Paper V also illustrates how naturalistic observational studies, like the HEADIS study, can be used when modelling costs and benefits from a particular intervention.

When analysing the cost-effectiveness of new treatments for a chronic disease like depression, it is important to assess the long-term consequences. In Paper V, health economic consequences were modelled from a hypothetical intervention over a time frame of five years. The projections were, however, based on assumptions of the long-term consequences of depression, not covered by empirical data. Relatively few studies have assessed the long-term risks of relapse and recurrence for depressed patients, and the HEADIS study was too short to provide this evidence. In order to verify the assumptions made in the model, long-term observational studies are needed.

In paper V, the Markov simulation model was used, since the pathology of depression may be summarized in a limited number of health states, which were both important from a clinical and economical perspective. The choice of modelling technique and the structure of the model is, however, always dependent on the data available for the analysis. The HEADIS study provided data on costs, quality of life and probability of remitting, and was suitable to populate the developed Markov model. Previous cost-effectiveness analyses in depression based on modelling have mainly used Markov or decision-tree models. It is, however, plausible that there will be a growing interest in the discrete event modelling technique in the future, since the management of the disease includes a variety of health disciplines, which are difficult to attribute to a certain health state in a Markov model or becomes too complex to structure in a decision-tree model. Discrete event modelling is, however, heavily data intensive, which needs to be collected before the strength of this technique may be used to its full extent.

All relevant costs and benefits should be included in an economic evaluation, but only once. If they are included more than once, a methodological problem may arise referred to as double-counting [127, 163]. There is a risk of double-counting when assessing the cost-effectiveness of interventions in depression, since the disease has a substantial impact both on quality of life and costs, and as treatments for depression also have impact on both. Double-counting could occur, for example, if a patient is absent from work due to her depression, and at the same time incorporates the income loss due to work absenteeism in the assessment of her health-quality of life. The risk of double-

counting is assumed to be relatively small in Sweden, as a large proportion of income losses due absenteeism are covered by the Swedish social security system. If income losses are relatively small for the individual, this may have little impact on health-related utility and thus, utility scores can be assumed to mainly include the actual impact of the depression. The ultimate way of eliminating the risk of double-counting should, however, not be to adjust for the two effects in the analysis (i.e. QALY loss and costs), but to incorporate it in the instructions for the assessment of the QALY weights employed in the analysis (i.e. no adjustment for income differences between the health states) [53]. This may be considered in future research.

Towards evidence-based health care

The analysis of the HEADIS study has shown that about half of patients treated for depression in primary care are relieved from their symptoms, during a follow-up period of six months. Similar findings have been reported from a survey of the Dutch primary care [159]. It is, thus, clear that there is room for improvements of how to treat and manage depressed patients in clinical practice. Until today, there are, however, relatively few clinical studies evaluating the safety and efficacy of therapies in the primary care setting [164], and very few observational studies evaluating the effectiveness of treatment in clinical practice. This provides an insufficient evidence for practicing doctors in their daily work with depressed patients. As stated in the Swedish health care law, health care should be provided on evidence-based grounds and the quality of health care should be routinely assessed [31]. With the evidence base available today there is no possibility to comply with this law in the care for depression, and until today only a few countries have established thorough treatment guidelines.

Today there is a widespread understanding that psychiatric registries are necessary to ensure effective and cost-effective care to patients. This was further emphasized by the installation of a national coordination of psychiatric care in Sweden in 2003, with the introduction of a specific project with the aim of initiating quality assessment tools in psychiatric care [165]. Pilot studies to such registries are already initiated for several psychiatric disorders, e.g. bipolar disorders [166], and national registries are already in place for other disease areas (e.g. osteoporosis). Along with the increased attention to quality assessments of psychiatric care in Sweden, the Swedish Board of Health and Welfare has initiated the work of producing guidelines for care of depression and anxiety. HEADIS is a one of the first health economic observational studies conducted in Sweden. The experience from the study could serve as an inspiration for future implementation of a national registry of care for depression, where health economic aspects should be included.

The present thesis indicates that better economic evaluations are needed to optimize the allocation of resources for care of depressed people. The quality of the economic evaluations depends on the quality of the data used in the analysis. So far there are few studies investigating the health economic consequences of depression based on sound real-life data, which makes future research necessary.

An even more challenging aspect of creating evidence-based mental health care for depressed people is the implementation of the results from economic evaluations. Although treatment guidelines do exist internationally, and growing economic evidence is available informing on which treatment strategies produce most health for money spent, there is an ongoing challenge to make health providers and doctors to incorporate this information in their daily practice. To succeed with this challenge there is a need for more transparency in the work of priority setting locally and quality assurance of health care provision, where national guidelines and quality registries are important instruments. There are a number of potential changes to improve the implementation of health economic evidence in practice: e.g. improved understanding and training in evidence-based medicine among doctors and other health providers, improved incentives in the health care provision (to avoid silo-budget problems) and increased transparency in national priority settings. The knowledge is still insufficient about what measures should be taken to improve the implementation of evidence-based medicine in clinical practice and what policies are needed to change medical practice, and thus are important topics for further research.

Suggestions for future research

In the present thesis, we have estimated the economic burden of depression in Europe. However, our estimates were partly based on assumptions as epidemiology and cost data on depression is still scarce in many European countries. To fully understand the societal costs of the disease it is necessary to conduct proper cost of illness studies, collecting information about resource-use and productivity in the individual countries. The epidemiology of depression is, furthermore, little investigated in the younger and older age groups of the population and by depression severity.

The present thesis has shown that about half of patients treated for depression in primary care are relieved from their symptoms. Hence, there is room for substantial improvements of how to treat and manage depressed patients in primary care. Until today, there are relatively few clinical studies evaluating the safety and efficacy of treatments in the primary care. Moreover, there is a need for further studies evaluating the effectiveness of both pharmacological and non-pharmacological treatments for depression in clinical practice.

The data collection on costs and quality-of-life in patients treated for depression in Sweden (HEADIS) was one of the first naturalistic observational studies conducted in a Swedish primary care setting. The study was, however, limited to a follow-up period of six months, and thus it would be desired to observe depressed patients over a longer time period in future studies. The HEADIS omitted the more severely depression patients, as no patients were recruited from the inpatient care setting, which should be included in future studies. It was not possible to fully investigate treatment patterns of pharmacological therapies for depression in the present observational study due to a too small a study population. Therefore, future research should use patient records in a more systematic way in order to improve the understanding of the management of depressed patients. A registry of how care is provided for depressed people, including health economic information, would be valuable source of data for future research.

In the results reported from the HEADIS study, only associations between different health states and costs and quality of life could be determined. A methodological challenge ahead lies in the analysis of casualties of data from observational studies which would provide more power in the conclusions drawn from the empirical evidence. There are a number of statistical techniques available which should be explored in future research.

There are very few studies evaluating the cost-effectiveness of treatments in Swedish health care and therefore, it is difficult to determine which treatments provide most health for money today, and in particular what patients should get which treatment. The cost-effectiveness analysis in the present thesis is an example of how to model health economic consequences for depression over time. There is a need for more systematic analysis of the cost-effectiveness of the available therapies for depression in order to optimize the allocation of resources for care for depression.

Little research has been conducted on mental health care policies and their health economic consequences and consequences for the quality of care. Furthermore, there is a need for more research on which measures are necessary to implement evidence-based medicine and open priority settings at local levels. There are several aspects that would need further investigation, such as the use of priorities and guidelines, training in evidence-based medicine, resource allocation and use of incentives in health care. The present thesis has also indicated the negative consequences of not treating patients to a symptom-free health state and to avoid recurrences. In comparison with somatic care programmes, more rigorous health care programmes should become available for psychiatric care directing how newly diagnosed patients with depression should be treated and managed in the long-run in order to avoid heavy burden on the individual and society.

CONCLUSIONS

The main conclusions from this thesis are:

- More than 21 million people suffer from depression in Europe and the disease costs European society more than SEK 1 000 billion per year in direct and indirect costs and is hence one of the single most costly diseases to society. The cost of depression corresponds to 1% of the European national incomes.
- The cost per depressed patient treated in primary care in Sweden was estimated at SEK 51 000 for six months 65% of which were due to indirect costs
- Depression reduces quality of life, measured with the generic a generic quality of life instrument (EQ-5D), by almost 50%, which is equal to the impact of a severe stroke. The reduction in quality of life is caused by an impact on several aspects of daily life such as usual activities, pain, discomfort, anxiety
- Direct and indirect costs increase and health-related quality of life decreases with depression severity
- Treating patients with depression to full remission reduces the cost and improves quality of life by 40% as compared to non-remitting patients, making remission an important aspect in the treatment and management of depressed patients
- Only half of the patients treated for depression in primary care become symptom-free which leaves room for further improvements of treatment and management models in clinical practice
- Clinical remission is a key parameter when modelling the health economic consequences of depression over time
- A simulation model estimated costs and health effects over 5 years of a patient treated for depression in Swedish primary care at SEK 157 700 and 3.62 QALYs.
- Naturalistic observational studies, such as the HEADIS study, provide important data for modelling the cost-effectiveness of treatments for depression
- Continuous follow-up how health care is provided to depressed patients is necessary to provide data for systematic studies and for evaluating health policies aimed at improving care for depressed patients

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