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Depression: Cost-of-illness Studies in the International Literature, a Review

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Abstract

Background: Depression is one of the most ancient and common diseases of the human race and its burden on society is really impressive. This stems both from the epidemiological spread (lifetime prevalence rate, up to 30 years of age, was estimated as greater than 14.4% by Angst *et al.*) and from the economic burden on healthcare systems and society, but also as it pertains to patient well-being.
Aims of the study: The scope of this review was to examine studies published in the international literature to describe and compare the social costs of depression in various countries.
Methods: A bibliographic search was performed on international medical literature databases (Medline, Embase), where all studies published after 1970 were selected. Studies were carefully evaluated and only those that provided cost data were included in the comparative analysis; this latter phase was conducted using a newly developed evaluation chart.
Results: 110 abstracts were firstly selected; 46 of them underwent a subsequent full paper reading, thus providing seven papers, which were the subject of the in-depth comparative analysis: three studies investigated the cost of depression in the USA, three studies in the UK and one study was related to Italy. All the studies examined highlight the relevant economic burden of depression; in 1990, including both direct and indirect costs, it accounted for US$ 43.7 billion in the US (US$ 65 billion, at 1998 prices) according to Greenberg and colleagues, whilst direct costs accounted for £417 million in the UK (or US$ 962.5 million, at 1998 prices), according to Kind and Sorensen. Within direct costs, the major cost driver was indeed hospitalization, which represented something in between 43 and 75% of the average per patient cost; conversely, drug cost accounted for only 2% to 11% in five out of seven studies.
Discussion: Indeed, our review suggests that at the direct cost level, in both the United States and the United Kingdom, the burden of depression is remarkable, and this is confirmed by a recent report issued by the Pharmaceutical Research and Manufacturers Association (PhRMA) where prevalence and cost of disease were compared for several major chronic diseases, including Alzheimer, asthma, cancer, depression, osteoporosis, hypertension, schizophrenia and others: in this comparison, depression is one of the most significant diseases, ranked third by prevalence and sixth in terms of economic burden. Moreover, in terms of the average cost per patient, depression imposes a societal burden that is larger than other chronic conditions such as hypertension, rheumatoid arthritis, asthma and osteoporosis. The application of economic methods to the epidemiological and clinical field is a relatively recent development, as evidenced by the finding that, out of the seven studies examined, three refer to the US environment, three to the UK and one to Italy, while nothing was available about the cost of depression for large countries such as France, Germany, Spain, Japan and others.
Implication for health care provision and use: The high incidence of hospitalization, and the finding that drug cost represents only a minor component of the total direct cost of the disease, suggests that room is still available for disease management strategies that, while effectively managing the patient's clinical profile, could also improve health economic efficiency.
Implication for health policies: Disease management strategies, with particular emphasis on education, should be targeted not only at patients and medical professionals but also at health decision makers in order 'to encourage effective prevention and treatment of depressive illness'.
Implications for further research: Cost of illness studies are a very useful tool allowing cost data comparisons across countries and diseases: for this reason, we suggest that further research is needed especially in some western European countries to assess the true economic burden of depression on societies.

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Introduction

Depression is often chronic, recurrent, and may be responsible for suicide attempts; according to the Epidemiological Catchment Area (ECA) study, its prevalence is high (9.5% lifetime prevalence). According to estimates by Greenberg *et al.*[2] in the year 1990 patients affected by depression were estimated to be approximately 11 million in the US. Most (71%) of these patients were women. According to Mendlewicz[3] depression is eight times more frequent than schizophrenia, and 16 times more frequent than Parkinson's disease. Another study in Zurich, carried out by Angst and colleagues, estimated a lifetime prevalence rate (up to 30 years of age) for depression greater than 14.4%, nearly twice as much as the rate calculated in the ECA study.

Depressed patients are at least as heavily disabled as patients affected by other chronic diseases such as hypertension, rheumatoid arthritis and diabetes. Their ability to fit

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into society is estimated to be worse. Mortality standard rates are higher, about twice, than in the general population.

These important elements highlight the size and the severity of the problem from a clinical perspective, but it is important to remember the impact on patients' perceptions and on their quality of life: 'people who suffer from depression usually experience as much or more limitations in multiple aspects of their daily functioning and well-being as is associated with most medical conditions'.[2]

Depression imposes a significant burden on industrialized countries both in terms of medical resources used to treat it and in terms of production losses due to work absenteeism, early retirement and premature mortality. The scope of this review was to provide a full and systematic picture of the data available in the international literature regarding the social costs of depression.

Methods of the Review

The bibliographic search was performed using Medline and Embase databases, including all works published after 1970 and considering the following key words: depression, cost-of-illness, indirect costs, pharmacoeconomics, and economic value. This first phase produced a total of 110 abstracts. These abstracts were analysed, in order to reject those containing treatment comparisons and those that did not supply cost data. Thus, 46 articles were selected (see the bibliographic section of this review for the full reference list). The second stage of the review was a full text reading of the 46 manuscripts to select only those articles that supplied information and analytic data on the cost-of-illness either as total cost referring to a specific population and/or country, or as average cost per patient. This evaluation produced a total of seven studies distributed as follows: three North-American studies;[2,4–6] three studies carried out in the United Kingdom[7–9] and research recently published in Italy.[10]

The last phase of this critical review was carried out using an appropriately designed chart which highlights basic information about the publication (author, journal and year of publication), and helps in the identification of the key elements of the research: the year and currency in which costs have been calculated; the population under study; the kind of analysis carried out; whether it contains detailed data on the level of severity of the disease or not; the data sources and details of the use of resources by typology of costs (direct versus indirect); the key results; and a synthetic comment. (A copy of the evaluation chart for each of the seven studies selected and discussed in this review is available from the authors upon request.)

Results

A discussion on the social cost of depression cannot ignore the problems relating to the epidemiological dimensions of the disease. In other words, the aspects of estimating the epidemiological impact are connected to the classification of the pathology. As a matter of fact, some authors, particularly in the North-American studies, specifically refer to epidemiological studies organized on the basis of diagnostic systems (DSM-III and DSM-III-R). Other authors, using joint national statistics, refer to depression without specifying whether they are analysing major depression or all of the syndromes summarized in the concept of 'depressive disorders'. In our discussion, the word depression will be used to refer to all the illnesses related to dysthymic disorders, while the term 'major depression' refers to specific codes (184, 185) of the DSM-IV.

The approach used in order to value costs appropriately represents a key difference between the studies. Cost analysis can be carried out using two different techniques: the top-down approach and the bottom-up approach. The main difference between the two methods is that in the former the cost of a population is calculated or estimated from national data and statistics in order to obtain the average cost of a single patient. In the bottom-up technique, starting from the consumption of resources at the patient's level, it is possible to value the cost of a sample of patients (possibly it should be representative of the population under analysis) in order to project, on a second step, the average value obtained, on a national scale (or on a population scale). In the selected studies, a top-down technique was used in the North-American studies as well as in those carried out in the United Kingdom. The bottom-up approach (starting from a group of patients selected and analysed according to the needs of a specific research protocol) was only used in the Italian study.

Social Costs of Depression in the US

Stoudemire *et al.*, 1986[4]

This is the first cost-of-illness study in the area of depression: published in 1986, it only examines major depression and it has been considered a reference point for researchers. It is a classic top-down approach study, starting from the epidemiological data of the ECA study and using national statistics in order to estimate the total costs.

In regard to mortality data, it is interesting to note that in previous studies the authors considered the number of suicides attributable to major depression to be about 60% of the total. This estimate translates into approximately 16 111 suicides per year caused by the disease, and a death rate equal to 7:100 000 subjects in the general population. It is important to note as well that the death rate calculated by the authors is remarkable at the 5–9 years age group (5.1:100 000), but it increases with age reaching 9.1–9.9:100 000 in people aged 20 to 64 years, and 10.65:100 000 in individuals aged 65 and older. Other authors will later make use of this percentage value of suicides attributable to major depression.

The portion of indirect costs which are non-productivity related, were estimated by Stoudemire *et al.* using several assumptions. These assumptions are: one day of absence from work for each day of admission to hospital, 0.25 day of absence from work for each outpatient examination, thus

yielding 156 million days off from paid work, lost in the entire population.

Stoudemire and colleagues have reckoned that major depression in 1980 was associated with a cost of US$ 16.3 billion (or US$ 52.7 billion, 1998).* Particularly, the higher share of costs is represented by the indirect costs (US$ 10 billion for non-productivity costs and US$ 4.2 billion for premature deaths), while direct costs (US$ 2.1 billion) only represent 13% of the total amount.

The average cost per patient, calculated on the basis of a population of 4.76 million people suffering from major depression, in 1980 was than about US$ 3400 per patient (US$ 11 000, 1998), a considerable value which, according to the authors, is 'for sure a conservative estimate'.

Rice and Miller, 1993[5]

Another study which is very important and, for some aspects, even more significant than the work by Stoudemire, was published by Rice and Miller in 1993. It is focused on the analysis of the costs related to affective disorders, which, according to DSM-III classification, include mania, depression and dysthymia.

The study is a cost-of-illness prevalence-based research, where top-down techniques were applied for cost estimation. Calculated values were based on national studies and statistics such as the NNHS (National Nursing Home Survey), the NIMH (National Institute for Mental Health); data relating to drug prescription were taken from the NPS (National Prescription Survey).

In regard to indirect costs, the authors used the following algorithm:

$$NPQV = \text{cost}$$

where N is the number of individuals affected in the population; P is the disease prevalence; Q is the amount of resources consumed; V is the monetary value applied to each resource (in US$). Consumption of resources refers both to the morbidity costs (costs generated by lost productivity due to the illness), and to mortality costs (deaths due to suicides), also reckoning lost productivity due to non-paid labour (mainly domestic labour of housewives).

In summary Rice and colleagues in 1990[11] found that the social burden due to affective disorders equals US$ 30.3 billion (or US$ 45.2 billion at 1998 prices). Direct costs represent a very high share—about 66%—which is then further divided as follows: 73% attributable to hospital costs (about US$ 14 000 billion) and 27% is represented by outpatient management (consultations and drugs).

Indirect costs represent about 34% of the total amount and can be ascribed to mortality (US$ 7700 billion) and to lost productivity (about US$ 2200 billion).

Greenberg *et al.*, 1993a,[2]b,[6] 1996[12]

From 1993 to 1996 Greenberg and colleagues published a series of works which marks a step forward in the assessment of the social burden of depression.

All these analyses of emotional disorders have been produced according to the DSM-III-R classification, which provides distinction among major depression (persistent mood and affective troubles), bipolar disorders (major depression and episodes of mania at the same time) and dysthymia (chronic condition characterized by depressed mood and by a general loss of interest and pleasure in activities).

Thus, data produced by Greenberg and colleagues relates to the whole of affective disorders and, again, are based on the epidemiological data of the ECA study; they estimated that in 1990 about 11 million people were affected, using the same methodology as applied by Stoudemire for 1980 population data.

This work is characterized as a retrospective analysis, using a top-down technique based on national statistics, and the evaluation of the indirect costs is based on the human capital approach. The human capital methodology estimates the value of lost labour time (because of the disease) by means of work payments, that is to say using the market price approach. What distinguishes the study by Greenberg from the others, is the evaluation, always made inside the indirect costs, not only of the sheer absenteeism (the labour day in which the patient is obliged not to go to work) but also of the so-called reduced productivity. That is to say the labour day in which the subject is at work but produces at a much lower rate because of symptoms. The amount of resources used for managing the disease was mostly drawn by the NIHM data, while costs were obtained by previously published statistics.

The global cost of the disease reported by this work was US$ 43.7 billion (or US$ 65 billion at 1998 prices). In the accompanying article,[6] the authors tried also to compare costs of depression to other major illnesses, highlighting that 'the cost of depression as calculated in the study ($44 billion) can be compared to the cost of heart disease ($43 billion), of AIDS ($66 billion) and of cancer ($104 billion)'.

Out of US$ 43.7 billion, direct costs (US$ 12.4 billion) represent less than a third (about 28%). Furthermore, it can be divided into hospitalization costs (US$ 8300 billion or 67% of direct costs) and outpatient management costs, within which drugs represent a total of US$ 1200 billion (about 10% of total direct costs). Indirect costs represent the most significant share (72%), where mortality holds 24% while the remaining 76% can be ascribed to the reduced or lost productivity.

Greenberg and colleagues, in a third article published in 1996, without changing direct costs calculation (which they believed still to be valid both for the methodology and for the reliability of sources), took advantage of the recent publication of the National Co-Morbidity Survey (NCS) data, in order to improve the assessment of the value of indirect costs. They calculated (in 1990 US dollars) that the total amount of indirect costs was not US$ 23.8 billion but

* Adjustment to 1998 US$ has been done using the Medical Consumer price index (Health in the United States, Centers for Disease Control, Atlanta, 1999).

US$ 33 billion, therefore total cost of the disease was re-calculated and rounded to US$ 55 billion (US$ 81.8 billion at 1998 prices).

Direct Costs of Depression in the United Kingdom

West, 1992[7]

In 1992, West, within a large report on epidemiological and clinical problems related to depression, tried to perform an assessment of the economic burden of this illness in the United Kingdom. West reports a consumption of antidepressant drugs of £55 million in 1990, based on published data. In contrast, hospitalization management cost, estimated to be £250 million was drawn from a previous OHE survey concerning all mental diseases. Depression accounted for 18% of all the admissions due to mental diseases. The cost of outpatient examinations performed by general practitioners, according to the author, was estimated from the more than 3.5 million visits (in England and Wales only), with an associated cost of about £28 million. These sums add up to a total cost of the disease of £333 million (US$ 769 million, 1998*).

Kind and Sorensen, 1993[9]

The data of Kind and Sorensen refer to a sub-population of the United Kingdom, defined by two geographical areas, England and Wales. The study was performed with reference to the year 1990.

In their basic hypothesis, the authors consider that out of 100 individuals affected by depression, 50% experience the disease once a year, 30% twice a year, while the remaining 20% experience multiple episodes. By applying this distribution to the different age groups drawn from the epidemiological data of the Royal College of General Practitioners, the authors estimated that in England and Wales 2.75 million episodes of depression are experienced each year. This implies that 7.39 million examinations are made by the general practitioners (in the outpatient setting and at patients' homes). Therefore, the total cost of all the examinations is more than £126 million. The number of hospital admissions was calculated on the basis of statistics from the Department of Health (i.e., more than 63000 admissions for acute hospital care); with the addition of a share of the admissions due to attempted suicides and antidepressant drug poisoning, the total cost of hospitalization was estimated to be £177 million. In regard to the cost of drugs, it was estimated to be about £47 million. This estimate is less than the cost of drugs estimated by West. The authors emphasize that the cost of drugs is only 11.3% of the total direct cost and that 'even with the advent of more expensive drugs this proportion is unlikely to exceed 15%—still well below the leading cost components'.

As to what pertains to the estimation of indirect costs, they considered the average length of the depressive episode; the average number of episodes in a given year; and the number of depressed subjects in the active population, thus obtaining an estimate of more than 155 million lost working days per year, or a value that exceeds £3 billion. Therefore, the total cost of the disease as calculated by these authors rounds up to £417 million (or US$ 963 million, 1998).

Jonsson and Bebbington, 1994[8]

This study is also based on a top-down technique, starting from the number of depressive episodes and unit cost, in order to calculate a global cost of the disease of about £222 million (or US$ 512.4 million, 1998). In particular, 19% of this cost can be ascribed to drugs, according to the Department of Health's data. Unfortunately, the elements provided for the reader are not explicit, making evaluation very difficult as compared to the results of the other British authors.

In discussing the results, the authors note that except for drugs, the costs are substantially underrated, particularly those relating to hospitalization and general practice.

Direct Costs of Depression in Italy

Tarricone, 1997[10]

The approach used in the Italian study of Tarricone, conducted with the GISIED (Gruppo Italiano di Studio sull'Impatto Economico della Depressione), is completely different from the previously described studies, because it is has been developed using a bottom-up technique. The scope of the project was to analyse the social costs of major depression both retrospectively and prospectively, using appropriately designed instruments, to collect health resource consumption data used in the management of the disease at the individual patient's level. The article analysed relates to the first retrospective portion of this two-phase research; the prospective research is ongoing.

According to an inclusion/exclusion protocol, all patients were recruited from psychiatric public departments, particularly psychosocial centres and diagnostic and treatment clinics of psychiatric disorders. The recruitment phase lasted 3 months, during which each clinic was required to recruit all referrals, up to a maximum number of ten patients per centre.

In the retrospective research, historical data were analysed, i.e., resource consumption by those patients suffering from episodes of major depression during the period prior to enrolment in the study. This resource consumption was estimated on the basis of patient reports. Every resource reported was suitably valued using market rates and prices. Results strictly refer to direct costs, as indirect costs will be valued only in the second phase of the study.

Cost data was presented according to the average cost of an episode of depression. This average cost is examined for two sub-samples, those without any previous episodes of depression (without PED) and subjects who already suffered from this disease (with PED). According to the author, the average cost of an episode of depression is Lit. 1016000

* Transformation to US$ has been performed using the UK Hospital and Community Health Services Inflation Index (HCHS) and the average exchange rate of 1998, i.e. US$ 1566 per pound sterling (source: http://www.oanda.com/converter/cc_table).

per patient (about US$ 650, 1998*). This estimate is quite similar in both groups: in patients with PED the cost is Lit. 1 020 000, while in patients without PED it is Lit. 1 018 000.

It is difficult to estimate the average cost per patient, beginning from a valuation of the average cost of an episode. Nevertheless, if hypothetically, an average patient experiences 2.5 episodes of major depression per year, this results in a cost of about Lit 2.5 million a year (or US$ 1603, 1998); of course these hypotheses should be confirmed or rejected by the prospective phase of this study.

Finally, in this work as well as in the others examined in this review, the considerable burden of hospitalization is highlighted, which alone accounts for about 70% of total direct costs, while antidepressant drug costs is a marginal share (about 6%).

Discussion and Conclusions

All the studies examined in this review highlight the relevant economic burden of depression.

The three North-American studies claim a considerable burden both in terms of direct and indirect cost. Clearly there are differences as regarding both total cost of the disease and the effect of the major cost drivers: it is important to understand these differences, in order to discuss their implications.

First, the work by Stoudemire only focused on major depression, concerning 4.7 million patients, while the analyses of both Rice and Millers' and Greenbergs' were based on much larger populations and examined all affective disorders.

Another difference between the two 1990 studies is the evaluation of direct costs and of productivity driven indirect costs. As for direct costs, explanations are not easy to venture: both studies are carried out using the same methodology and were based on national statistics. As a matter of fact, hospitalization is the most relevant driver of the difference (perhaps in terms of a different method to calculate both units and values for hospital admissions). Both studies concur on the importance of hospitalization in so far that the variation noted also influences direct costs as a whole.

Differences exist in the comparison of indirect costs as well: Greenberg enlarged his analysis of lost productivity due to the disease, including the value of time spent at work while suffering from depression; this could be one explanation for the value reported in his study being considerably higher.

This disease carries a considerable epidemiological impact, and is often misdiagnosed and mistreated as well. As the NIHM Consensus Conference claims, 'depression imposes an enormous burden on society—resulting from its high prevalence, under-diagnosis and under-treatment. Depression has many costs and consequences, including decreased quality of life for patients and their families, high morbidity and mortality, and substantial economic losses'.

Recently, in a report by the Pharmaceutical Research and Manufacturers Association[13] the cost of depression has been compared to other major chronic diseases. In **Figure 1** prevalence and total management costs of diseases such as Alzheimer, asthma, cancer, depression, osteoporosis, hypertension, schizophrenia and others are presented.

As seen in this comparison, depression is one of the most significant diseases, ranked third by prevalence and sixth in terms of economic burden. Moreover, in terms of the average cost per patient, depression imposes a societal burden that is larger than other chronic conditions such as hypertension, rheumatoid arthritis, asthma and osteoporosis (see **Figure 2**).

Indeed, this analysis suggests that at the direct cost's

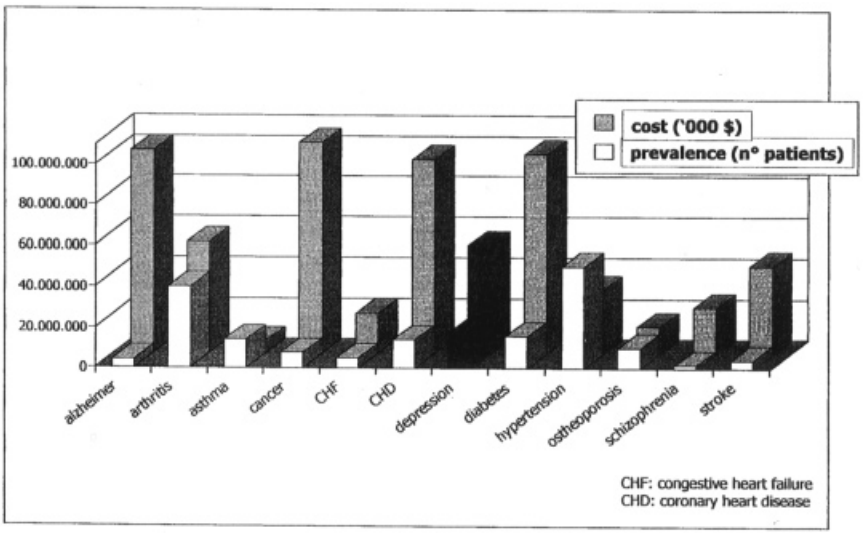

Figure 1. USA—prevalence and cost of major chronic conditions

* Transformation to US$ has been performed using the Italian Consumer Price Index and the average exchange rate of 1998, i.e. Lit/US$ (Banca d'Italia, 1999).

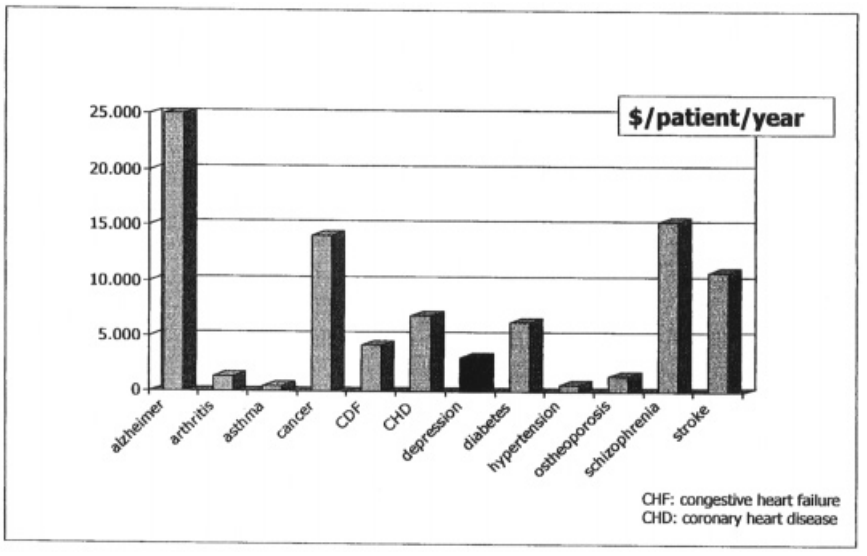

Figure 2. USA—cost/patient/year of selected major conditions

level, both in the United States and the United Kingdom the burden of depression is remarkable.

Taking a step further, one can also compare not only the absolute values (the total cost of disease or the average cost per patient) but, rather the pattern of cost distribution among the most relevant variables. This distribution is presented in **Figure 3**.

It is apparent that within the direct cost estimation, the most significant cost driver is undoubtedly hospitalization. Hospitalization commands the highest share in all the studies, varying from 43–52% in both UK studies by Kind and Sorensen and by Johnson and Bebbington, to 73–75% in the studies by Rice and Miller and by West.

Another common aspect for all the studies is the relatively small social burden represented by drugs, whose effect on total cost is limited, being between 2% and 11% in five out of seven studies.

The high cost represented by depression with regard to the health system, is borne out in an analysis carried out by Simon and colleagues. This work examined the cost of managing patients (age $\geq$18), visited at a large Health Maintenance Organization (HMO); direct healthcare costs for 6257 patients suffering from depression were collected and compared to the same number of controls (matched by age and gender). Results can be summarized as follows: depressed patients cost 1.8 times more than controls; particularly they generate costs twice as large for specialist's outpatient visits, and at least 1.5 higher for all other variables (admissions, emergency care, drugs).

Also, the study by Unuzer and colleagues[15] focusing on patients aged 65 years or older, revealed that (among 2558 subjects recruited at four HMOs) 'in this cohort of older adults, depressive symptoms were common, persistent and associated with a significant increase in the cost of general medical services. This increase was seen for every component of health care costs and was not accounted for by an

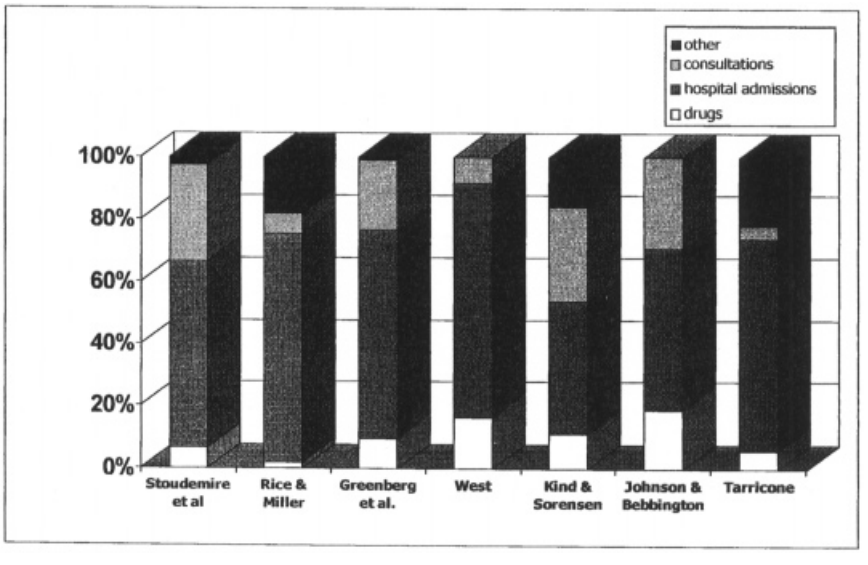

Figure 3. Direct costs—seven studies

increase in specialty mental health care. The increase in health care costs remained significant after adjusting for differences in age, sex and chronic medical illnesses'.

This review has shown that in Europe only a few studies are available about the cost-of-illness of depression, including the three UK studies and the Italian study. As a matter of fact some additional qualitative data is available.

For example, a study published in France[16] carried out in six different European countries (UK, Belgium, France, Germany, Holland and Spain) presented comparative data about consumption of resources in patients with and without depression. Indeed, this study showed that subjects suffering from major depression needed to consult their GP more frequently than controls (4.4 versus 1.5 visits during a 6 month period) and also more frequently than those who suffer from minor depression and depressive symptoms (4.4 versus 2.9 and 3.0 visits respectively). Also, the number of lost working days was considerably higher: 12.7 for people affected by major depression compared with 10.2 in the group suffering from minor depression, 4.1 for those with depressive symptoms and 2.9 for controls. Finally, another interesting finding is related to the use of drugs: only 31% out of 5400 patients suffering from major depression reported being treated with a drug prescribed by a doctor. The authors conclude, 'the results suggest the need for educational programmes directed at subjects in the community as well as physicians and health authorities to encourage effective prevention and treatment of depressive illness.'

The theme of the education of patients and doctors is also part of a wider perspective of the disease management of depression which is a sensitive issue particularly in the US environment. As a matter of fact one of the most important conclusions of the Consensus Conference of NIMH[17] states verbatim: 'the shift of even a small portion of the... indirect costs into direct treatment costs, could produce a profound improvement in the lives of those currently untreated and under-treated'.

Thus, for depression as well as other major chronic illnesses, it is important to consider global disease management. Hence, a proper use of all the remedies available to date can really improve not only the clinical but also the economic component of the management of patients suffering from depression, thus producing global savings for the health system.

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