Yi-Ju Pan, Martin Knapp, Ling-Ling Yeh, Yu-Pei Chen and Paul McCrone

Treatment costs for depression with pain and cardiovascular comorbidities

Article (Accepted version) (Refereed)

Original citation:
Pan, Yi-Ju, Knapp, Martin, Yeh, Ling-Ling, Chen, Yu-Pei and McCrone, Paul (2013) *Treatment costs for depression with pain and cardiovascular comorbidities.* Journal of psychiatric research, 47 (3). pp. 329-336.
DOI: 10.1016/j.jpsychires.2012.11.005

Treatment costs for depression with pain and cardiovascular comorbidities

Yi-Ju Pan, M.D., M.Sc. [a,b], Martin Knapp, Ph.D. [a,c], Ling-Ling Yeh, Ph.D. [d,*] , Yu-Pei Chen, M.Sc. [d], Paul McCrone, Ph.D. [a]

[a] Centre for the Economics of Mental and Physical Health, Health Service and Population Research Department, Institute of Psychiatry, King's College London, United Kingdom

[b] Department of Psychiatry, Far Eastern Memorial Hospital, Taiwan

[c] Personal Social Services Research Unit, LSE Health and Social Care, London School of Economics and Political Science, United Kingdom

[d] Department of Healthcare Administration, Asia University, Taiwan

[*]Corresponding author.
E-mail address: yehll.sophia@msa.hinet.net (L.L.Yeh).
Tel: 886-4-23323456 ext 1807
Fax: 886-4-23394588
Address: 500, Lioufeng Rd., Wufeng, Taichung, Taiwan 41354

Abstract

Objective: As depressive disorders are highly heterogeneous, and as patients exhibit wide differences in clinical characteristics and comorbidities, we aim to examine whether and how demographic and clinical correlates affect healthcare costs for patients with depression in a real-world setting.

Method: A national cohort of adult patients (n=216,557) who received treatment for depression was identified from the National Health Insurance Research Database in Taiwan. Factors associated with service use and healthcare costs over a 12-month period were explored, with a particular focus on past treatment history, comorbid physical illnesses, painful physical symptoms, and choice of initial antidepressants.

Results: Depression severity, past treatment history, comorbid mental/physical illnesses, painful physical symptoms, and choice of initial antidepressants were found to be associated with healthcare costs in the following year, although the nature of the associations differed across cost categories. The presence of comorbid cardiovascular disease or certain painful physical symptoms at baseline was associated not only with higher non-psychiatric but also with higher psychiatric costs; moreover, patients with these comorbidities were shown to have increased use of psychiatric emergency and inpatient services.

Conclusion: Healthcare costs for depression are affected by a number of clinical characteristics and comorbidities of patients. The importance of comorbid pain and cardiovascular conditions warrants further research.

Keywords: depression; cost; pain; cardiovascular disease; comorbidity

1. Introduction

Unipolar depressive disorder was the fourth leading cause of disease burden among all diseases in 2002 (Mathers and Loncar, 2006) and is predicted to become the leading cause in 2015 (WHO 2008). The total direct healthcare costs of depression in Taiwan, as in many other countries, rose by 50% over the period of 2000-2002 (Chan et al., 2006); the prevalence of antidepressant use also doubled from 1997 to 2004 (Chien et al., 2007). This could imply an increase in the need for depression treatment, a reduction in the treatment gap, or over-provision of care. Given the anticipated rise in the future healthcare costs for patients with depression, it would help inform decision-making to assess the impact of depression treatment from an economic perspective.

Depressive disorders comprise a group of heterogeneous conditions. The extent to which treatment history, comorbidities of physical/mental illnesses, and choice of antidepressants can influence healthcare costs remains to be determined. Depression is known to be associated with a variety of physical conditions (Katon 2003) of whom cardiovascular diseases (CVD) and painful physical symptoms (PPS) warrant further investigation. Depression and CVD are projected to be the first and second leading causes of health-related burden in 2015 (WHO 2008), and there is accumulating evidence suggesting close interrelationships between these highly-prevalent conditions (Sorensenf et al., 2005; Thombs et al., 2006): for instance, depressive symptoms have been found to be a risk factor for cardiac events in patients with coronary heart disease (Barth et al., 2004; van Melle et al., 2004). To assess the economic impact of treatment for depression, PPS should also be carefully considered. Previous studies have revealed high prevalence of pain complaints in depressed patients (Bair et al., 2003; Husain et al., 2007; Ohayon and Schatzberg, 2003) and outcomes of treatment for depression may be poorer in the presence of PPS (Fava et al., 2004; Gameroff and Olfson, 2006; Leuchter et al., 2010). Furthermore, individual antidepressants have been shown to have a wide range of cardiovascular effects (Taylor 2008), and antidepressants may differ in the effectiveness for the relief of PPS. Therefore, the presence of these co-occurring CVD and PPS may influence the choice of antidepressants and healthcare utilization, with potential impact on healthcare costs.

The current study, conducted in a real-world setting, seeks to measure healthcare costs for people with depression using claims data from the National Health Insurance Research Database (NHIRD) in Taiwan. The objective of this study is to identify which demographic and clinical characteristics and comorbidities are associated with total healthcare costs, as well as costs for specific groups of services, with a particular focus on comorbid pain and cardiovascular diseases.

2. Materials and methods

2.1. Data

Taiwan is a country with a population of around 23,000,000. The GDP per capita in 2003/2004 was 13,773/15,012 US dollars. National Health Insurance (NHI) in Taiwan is a single-payer compulsory social insurance plan that centralizes the disbursement of healthcare funds and guarantees equal access to health care for all citizens. In 2003, there were 21,869,478 individuals enrolled in the NHI with a coverage rate of 96%. The NHI contracted 17,022 medical institutions, which constituted 93.8% of medical institutions nationwide. By the end of 2005, approximately 22.7 million individuals had been enrolled in Taiwan's NHI program

with a coverage rate of 98%. The NHI system in Taiwan contains the NHIRD which consists of data characterizing healthcare utilization of insured residents, including expenditures, medical procedures/treatments, and basic characteristics of patients, providers and physicians. The NHIRD uses the International Classification of Diseases, 9th revision, clinical modification diagnoses (ICD-9-CM).

In this study, the included subjects were identified from the NHIRD. The index date was defined as the date on which the subject was first prescribed an antidepressant for a diagnosis of depressive disorder in 2003. Data on all NHI information for each subject were extracted for the two-year period spanning the index date (one year preceding, and one year following).

2.2. Participants

All subjects in NHIRD meeting the following criteria were included:

- At least one prescription for an antidepressant for treatment of major depressive disorder (MDD) (ICD-9-CM codes: 296.2x, 296.3x) or minor depression (ICD-9-CM codes: 311.xx, 300.4x) in 2003.
- Data available for a minimum of 12 months before and after the index date.
- Age 18 years or over on the index date.

A subsample of patients with *newly-diagnosed depression* was also identified within this overall sample, which was operationally defined as individuals who were free of antidepressant use or a depression diagnosis for a minimum of 12 months before the index date.

2.3. Demographic and clinical information

Demographic and clinical data were extracted, including age, gender, diagnosis of depressive disorders, and initial choice of antidepressants on the index date. Participants were further grouped according to past treatment history, i.e., newly-diagnosed depression and non-newly-diagnosed depression.

Baseline characteristics were traced back for all subjects for the 12 months prior to the index date, including comorbid mental disorders, physical illnesses (CVD, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), renal diseases, and cancer), PPS (backache, headache, musculoskeletal and gastrointestinal pain), and healthcare utilization/expenditure.

2.4. Service use and costs

Service use components extracted from the NHIRD included outpatient services, emergency attendances, and inpatient stays. Service use over the 12-month study period was described by the percentage of patients with at least one unit of service use and the mean number of service contacts for the whole sample. Medication use regarding prescriptions of antidepressants was identified. All costs over the 12-month study period were calculated from the actual claims data, were described by service categories, and expressed in 2003-4 US dollars.

2.5. Data analysis

Sociodemographic data, clinical characteristics, baseline healthcare utilization/expenditure, and initial antidepressant treatment were described for the overall sample and compared between newly-diagnosed depression and non-newly-diagnosed depression groups.

To identify characteristics predictive of healthcare costs over the 12-month period, a multivariate generalized linear regression model with a log link and gamma

variance function was employed (McCullagh and Nelder, 1989). Separate models were run for total healthcare costs, psychiatric costs, and non-psychiatric costs. And to measure the model fit, the root mean square error (RMSE) (Zheng and Agresti, 2000) for each model was computed after excluding 0.1% of subjects with extremely large predicted values in costs. The independent variables considered in these models were age, sex, index depression diagnosis, past treatment history, initial choice of antidepressants, baseline comorbid mental/physical disorders, baseline PPS, and baseline total healthcare expenditure. These variables were first selected using a univariate model and those significant at the 5% level were included subsequently. A backward selection process was then applied to obtain the final multivariate model, using a 5% level of significance. Subsequently, such analyses were performed in a subsample of subjects with newly-diagnosed depression as they were a group which warrants further investigation. This was also to determine the influence of past treatment history on the findings from the overall sample.

As use of psychiatric emergency and/or inpatient services may be indicators for patients who require more intensive care, thus generating higher costs, we examined variations in use of these two key services in further analyses. With use of psychiatric emergency services and use of psychiatric inpatient services as dependent variables, independent variables were entered in a multivariate logistic regression with a forward LR (likelihood ratios) method to explore predictors of use over the 12-month study period. A p-value of 0.05 was considered significant for all statistical analyses, which were performed using SPSS version 17.0 (Chicago, IL, USA).

3. Results

A total of 216,557 adult individuals met the inclusion criteria, including a subsample of 84,577 persons with newly-diagnosed depression. Table 1 shows that for the overall sample, 61.9% were females and 18.7% were aged 65 years or over on the index date. Regarding baseline comorbidities, 26.9% had CVD, 10.9% had DM, and 15.2% had COPD. Comorbid PPS rates were particularly high for both the overall sample and the subsample of individuals with newly-diagnosed depression. At the index visit, 45.6% of the overall sample were prescribed selective serotonin reuptake inhibitors (SSRIs) and 8.6% prescribed serotonin norepinephrine reuptake inhibitors (SNRIs). Only 3.1% of patients received other newer antidepressants (bupropion and mirtazapine).

Patients with newly-diagnosed depression were younger and had a greater proportion of females compared to those with non-newly-diagnosed depression. They had lower rates of comorbid physical/mental illnesses and lower prevalence of PPS. Health service utilization at baseline was lower as well. A higher proportion of them were prescribed newer generation antidepressants.

3.1. Service use and costs

Service use data are summarized in Table 2. Of the overall sample, 85.1% had used psychiatric outpatient services over the 12-month study period. Over the same period, 5.0% of them had been admitted to psychiatric wards for inpatient treatment and 1.6% had psychiatric emergency attendances.

Costs of outpatient contacts in total accounted for 63.6% of total healthcare costs for these patients. And overall expenditures on psychiatric services were around 29.2% of the total healthcare costs.

3.2. Total healthcare costs

Table 3 reveals that higher total healthcare costs were associated with older age, male gender, an index diagnosis of MDD, non-newly-diagnosed depression, and having CVD, DM, COPD, renal disease, cancer or PPS at baseline.

Use of SNRIs, other newer generation antidepressants and use of multiple antidepressants were related to higher costs compared to use of SSRIs at the index date. Lower costs were observed for those using tricyclic antidepressants (TCAs), flupentixol/melitracen, and other older antidepressants (maprotiline, moclobemide, and trazodone). The analysis on the subsample of newly-diagnosed depression revealed similar results with those from the full sample. Regarding the model fit, RMSE of the model for total costs was 1316. The predicted mean of total costs was 1925 US dollars versus the actual mean costs 1731 US dollars.

3.3. Non-psychiatric healthcare costs

Older age, and male gender were related to higher non-psychiatric costs in the following year (Table 4). Compared to patients with history of either an antidepressant treatment or a depression diagnosis, those with newly-diagnosed depression had higher non-psychiatric costs. Patients with an index diagnosis of MDD or a baseline comorbid mental disorder were associated with lower costs, with the only exceptions being alcohol, substance misuse, multiple drugs-related mental disorders and dementia. The presence of a comorbid physical illness or PPS at baseline was related to higher non-psychiatric costs.

Patients prescribed older antidepressants had higher non-psychiatric costs in the following year compared to those prescribed SSRIs while patients prescribed newer antidepressants such as SNRIs or bupropion/mirtazapine had non-psychiatric costs that did not differ significantly. The RMSE of the model was 4380. And the predicted mean of non-psychiatric costs was 1452 US dollars while the actual mean cost was 1226 US dollars.

3.4. Psychiatric healthcare costs

As shown in Table 4, male gender was associated with higher psychiatric costs in the following year. Not surprisingly, patients having an index diagnosis of MDD had increased costs as did those with baseline comorbid mental disorders. Patients with newly-diagnosed depression had lower psychiatric costs compared to those who had been diagnosed prior to the index date. Younger age was shown to be related to *higher* psychiatric costs.

Use of newer generation antidepressants or multiple antidepressants prescribed on the index date were related to higher psychiatric costs compared to those prescribed SSRIs, while use of older antidepressants was related to lower costs. Among comorbid physical illnesses, CVD was the only one found to increase psychiatric costs. And among PPS, only pain complaints relating to the central nervous system (CNS), i.e., headache/dizziness/or migraine, were related to higher psychiatric costs. The RMSE of the model was 1074. The predicted mean of psychiatric costs was 577 US dollars and the actual mean was 506 US dollars.

3.5. Use of psychiatric emergency and inpatient services

Younger age, male gender, a diagnosis of MDD or certain comorbid mental disorders were more likely to lead to psychiatric emergency attendances and hospitalizations (Table 5). CVD or COPD was related to higher odds of using psychiatric emergency and hospitalization services. Headache/dizziness/or migraine complaints at baseline were associated with an increase in the odds of using

psychiatric emergency and hospitalization services as well.

4. Discussion

This study provided new evidence on the associations between comorbidities, service use, and healthcare costs for patients with depression. Although the nature of the associations differed across cost categories, the multivariate models revealed that age, gender, depression severity, past treatment history, comorbid mental/physical illnesses, PPS, and choice of initial antidepressants were all associated with healthcare costs in the following year. Factors including comorbid CVD and PPS were further explored to understand patterns of variation in psychiatric emergency and inpatient service use over the 12-month study period.

4.1. Demographic characteristics

Although previous studies have suggested that medical costs are higher for women than men (Owens 2008; Woolhandler and Himmelstein, 2007), this study found a different result: for patients with depressive disorders, and taking into account other influences on costs, male gender was shown to be associated with higher costs for both non-psychiatric and psychiatric healthcare services.

There have been few recent studies that specifically examined the association between gender and healthcare utilization/expenditure for patients with depressive disorders. A study of elderly patients with psychiatric diagnoses suggested that men had more emergency attendances and had greater inpatient costs than women, which led some investigators to propose that when men eschew regular visits to physicians, it is likely that emergency or inpatient treatment may be required as illness progresses (Husaini et al., 2002). Consistently, male patients were shown to be associated with increased use of psychiatric emergency and inpatient services in the current study. One interpretation of our results is therefore that male patients with depression may enter the healthcare system later in the disease course, by which time their illness is more severe, thus generating higher costs.

4.2. Comorbid cardiovascular disease

Among the frequently co-occurring physical illnesses considered in this study, CVD was the only one shown to increase not only non-psychiatric but also psychiatric costs. Depression has been revealed to be an independent risk factor for the future onset, progression, and recurrence of CVD (Carney et al., 1988; Ferketich et al., 2000; Nicholson et al., 2006; Rugulies 2002; Sesso et al., 1998; Wassertheil-Smoller et al., 2004), which can be mediated both by poor health behavior and by the pathophysiological correlates of depressive symptoms, e.g., neuroendocrine and inflammatory activation (Frasure-Smith and Lesperance, 2010; Rozanski et al., 2005). Additionally, individual antidepressants have a wide range of cardiovascular effects which may affect cardiovascular-related morbidity and mortality (Coupland et al., 1997; Taylor 2008; Vieweg and Wood, 2004); it seems likely that the co-existence of CVD and depression may impact patients' physical conditions and their non-psychiatric costs.

As well, we found that the presence of comorbid CVD was related to higher odds of using both psychiatric emergency and hospitalization services which was consistent with the finding of increased psychiatric costs in these patients. CVD has been shown to be correlated with certain lifestyles, alcohol consumption, and personality traits (e.g., Type D personality), some of which seem to be highly correlated with use of psychiatric services. For instance, Type D has been conceptualized as a personality

trait comprising negative affectivity and social inhibition that often co-occurs with depression in patients with coronary artery disease, and that may inhibit remission of depressive symptoms (Albus et al., 2011; Denollet et al., 2010). Although it can only be speculative, the identified association between the presence of CVD and increased psychiatric service utilization/expenditure in this study may be understood as being indirectly influenced by these unmeasured and potentially associated factors.

4.3. Painful physical symptoms

The relationships between depression and pain are complex with similar brain areas regulating both mood and the affective components of pain (Giesecke et al., 2005). High prevalence of pain complaints has been reported in patients with depression (Bair et al., 2003; Husain et al., 2007; Ohayon and Schatzberg, 2003). Our results added to this evidence in finding a high percentage of comorbid PPS in patients with newly-diagnosed depression, which supports findings from previous studies that pain usually appears before the development of MDD (Ohayon and Schatzberg, 2010). On the other hand, increasing pain interference has been reported to be associated not only with higher odds of having depressive disorders (Barry et al., 2012), but also with adverse impact on poor treatment response (Bair et al., 2004). Pain complaints seem to be characteristic of depression that is more severe and refractory to antidepressant treatments, as evidenced by higher healthcare utilization, and higher costs (Gameroff and Olfson, 2006).

As most previous studies were based on highly selective samples and did not consider many comorbidities, it is unclear whether these results could be generalized to larger samples of patients in a real-world setting, and to what extent other factors such as comorbid mental/physical illnesses would contribute to the possible association between PPS, healthcare utilization, and treatment outcome. In the current study, we concurred with previous studies in suggesting that the presence of PPS was associated with higher total healthcare costs in the following year; this remained true for those with newly-diagnosed depression. In addition, analyses based on origins of pain complaints found that the co-existence of PPS was generally associated with higher non-psychiatric costs but lower psychiatric costs, with headache being the only exception: unlike pain complaints over other somatic systems, having headache was associated with higher psychiatric costs and greater odds of using psychiatric emergency and inpatient services. A recent study suggested the existence of differences in separate pain modalities in relation to depression, and that a closer relationship may exist between MDD and neuropathic pain than non-neuropathic pain (Ohayon and Stingl, 2012). It seems possible that a more direct relationship might exist between depression and pain complaints over the central nervous system than PPS from other somatic systems as our data might suggest.

4.4. Antidepressant choice

The current study showed that initial choice of antidepressants appears to be associated with total healthcare costs in the following year. Compared to patients prescribed SSRIs, those prescribed older antidepressants had lower total and psychiatric costs, whilst patients prescribed SNRIs, and other newer antidepressants had higher total and psychiatric costs. However, to a large extent these differences may be attributed to physician selection: patients prescribed older antidepressants were more likely to suffer minor depression, to be older, and to have more PPS and physical comorbidities at baseline. Contrarily, patients prescribed newer antidepressants were more likely to have MDD, to be younger, and to have fewer

baseline physical comorbidities (not shown in this paper). These distinctive characteristics suggest the existence of physician selection based on patients' clinical characteristics that unfortunately could not be fully accounted for by the adjustment factors in our analyses.

Further support could be drawn from the comparisons between cost models: as seen in Table 4, patients prescribed SNRIs and other newer antidepressants were similar to those prescribed SSRIs in non-psychiatric costs, whilst patients prescribed TCAs and other older antidepressants generally had higher non-psychiatric costs. These results could be interpreted as showing that there were differences especially in physical comorbidities between these two groups of depressed patients. Previous database analyses have also suggested that SSRI users may have higher depression-related service expenditures but lower non-depression-related service expenditures than TCA users (Pan et al., 2012). Along with these previous findings, our results suggest that depressed patients prescribed older antidepressants may be different from those prescribed SSRIs, SNRIs, and other newer antidepressants in terms of clinical features of depression and comorbidities.

4.5. Limitations and conclusions

As service use data contained in the NHIRD includes only health services provided by the NHI system in Taiwan, the perspective of the current analysis was relatively limited, and we were not able to analyze wider economic impacts. Confounding or selection bias due to the nonrandomized study design should be borne in mind while interpreting the results, although the real-world context and whole-country coverage are strengths, especially when analyzing the inherent heterogeneity of clinical presentations and patient characteristics and their influences on help-seeking behaviors, clinical outcomes, and costs.

In conclusion, the current study—based on a large national database—suggests a set of significant correlates of healthcare costs for depressed patients. Male gender and a diagnosis of MDD were significantly associated with higher total healthcare costs. The baseline comorbidities of CVD and headache were associated not only with higher non-psychiatric but also with higher psychiatric costs; moreover, these comorbidities were related to increased use of psychiatric emergency and inpatient services in the following year.

References

Albus C, Beutel ME, Deter HC, Fritzsche K, Hellmich M, Jordan J, et al. A stepwise psychotherapy intervention for reducing risk in coronary artery disease (SPIRR-CAD) - rationale and design of a multicenter, randomized trial in depressed patients with CAD. Journal of Psychosomatic Research 2011;71:215-22.

Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. Psychosomatic Medicine 2004; 66:17-22.

Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Archives of Internal Medicine 2003;163:2433-2445.

Barry DT, Pilver C, Potenza MN, Desai RA. Prevalence and psychiatric correlates of pain interference among men and women in the general population. Journal of Psychiatric Research 2012;46:118-27.

Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosomatic Medicine 2004;66: 802-13.

Carney RM, Rich MW, Freedland KE, Saini J, teVelde A, Simeone C, et al. Major depressive disorder predicts cardiac events in patients with coronary artery disease. Psychosomatic Medicine 1988;50:627-33.

Chan AL, Yang TC, Chen JX, Yu LH, Leung HW. Cost of depression of adults in Taiwan. The International Journal of Psychiatry in Medicine 2006;36:131-5.

Chien IC, Bih SH, Chou YJ, Lin CH, Lee WG, Chou P. Trends in the use of psychotropic drugs in Taiwan: a population-based national health insurance study, 1997-2004. Psychiatric Services 2007;58:554-7.

Coupland N, Wilson S, Nutt D. Antidepressant drugs and the cardiovascular system: a comparison of tricylics and selective serotonin reuptake inhibitors and their relevance for the treatment of psychiatric patients with cardiovascular problems. Journal of Psychopharmacology 1997;11:83-92.

Denollet J, Schiffer AA, Spek V. A general propensity to psychological distress affects cardiovascular outcomes: evidence from research on the type D (distressed) personality profile. Circulation: Cardiovascular Quality and Outcomes 2010;3:546-57.

Fava M, Mallinckrodt CH, Detke MJ, Watkin JG, Wohlreich MM. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? Journal of Clinical Psychiatry 2004;65:521-30.

Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML. Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey. Archives of Internal Medicine 2000;160:1261-8.

Frasure-Smith N, Lesperance F. Depression and cardiac risk: present status and future directions. Heart 2010;96:173-6.

Gameroff MJ, Olfson M. Major depressive disorder, somatic pain, and health care costs in an urban primary care practice. Journal of Clinical Psychiatry 2006;67:1232-9.

Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis & Rheumatism 2005;52:1577-84.

Husain MM, Rush AJ, Trivedi MH, McClintock SM, Wisniewski SR, Davis L, et al. Pain in depression: STAR*D study findings. Journal of Psychosomatic Research 2007;63:113-22.

Husaini BA, Sherkat DE, Levine R, Bragg R, Holzer C, Anderson K, et al. Race, gender, and health care service utilization and costs among Medicare elderly with psychiatric diagnoses. Journal of Aging and Health 2002;14:79-95.

Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biological Psychiatry 2003;54:216-26.

Leuchter AF, Husain MM, Cook IA, Trivedi MH, Wisniewski SR, Gilmer WS, et al. Painful physical symptoms and treatment outcome in major depressive disorder: a STAR*D (Sequenced Treatment Alternatives to Relieve Depression) report. Psychological Medicine 2010;40:239-51.

Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Medicine 2006;3:e442.

McCullagh P, Nelder J. Generalized Linear models. London: Chapman and Hall, 1989.

Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146538 participants in 54 observational studies. European Heart Journal 2006;27:2763-74.

Ohayon MM, Schatzberg AF. Chronic pain and major depressive disorder in the general population. Journal of Psychiatric Research 2010;44:454-61.

Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. Archives of General Psychiatry 2003;60:39-47.

Ohayon MM, Stingl JC. Prevalence and comorbidity of chronic pain in the German general population. Journal of Psychiatric Research 2012;46:444-50.

Owens GM. Gender differences in health care expenditures, resource utilization, and quality of care. Journal of Managed Care Pharmacy 2008;14:2-6.

Pan YJ, Knapp M, McCrone P. Cost-effectiveness comparisons between antidepressant treatments in depression: Evidence from database analyses and prospective studies. Journal of Affective Disorders 2012;139:113-25.

Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. Journal of the American College of Cardiology 2005;45:637-51.

Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. American Journal of Preventive Medicine 2002;23:51-61.

Sesso HD, Kawachi I, Vokonas PS, Sparrow D. Depression and the risk of coronary heart disease in the Normative Aging Study. American Journal of Cardiology 1998;82:851-6.

Sorensenf C, Friis-Hasche E, Haghfelt T, Bech P. Postmyocardial infarction mortality in relation to depression: a systematic critical review. Psychotherapy and Psychosomatics 2005;74: 69-80.

Taylor D. Antidepressant drugs and cardiovascular pathology: a clinical overview of effectiveness and safety. Acta Psychiatrica Scandinavica 2008;118:434-42.

Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, et al. Prevalence of depression in survivors of acute myocardial infarction. Journal of General Internal Medicine 2006;21:30-8.

van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosomatic Medicine 2004;66: 814-22.

Vieweg WV, Wood MA. Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. Psychosomatics 2004;45:371-7.

Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, et al. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). Archives of Internal Medicine 2004;164:289-98.

WHO. Projections of mortality and burden of disease, 2004-2030. http://www.who.int/healthinfo/global_burden_disease/projections/en/index.html. retrieved on 3 Feb 2012

Woolhandler S, Himmelstein DU. Consumer directed healthcare: except for the healthy and wealthy it's unwise. Journal of General Internal Medicine 2007;22:879-81.

Zheng B, Agresti A. Summarizing the predictive power of a generalized linear model. Statistics in Medicine 2000;19:1771-81.

Formatted: Left: 2.54 cm, Right: 2.54 cm, Top: 3.17 cm, Bottom: 3.17 cm, Width: 29.7 cm, Height: 21 cm

Table 1. Sociodemographic and clinical characteristics of the overall sample and comparisons between newly-diagnosed and non-newly-diagnosed depression*

	The overall sample (n=216,557)	Newly-diagnosed depression (n=84,577)	Non-newly-diagnosed depression (n=131,980)
Age [mean (SD)]	47.4 (17.0)	43.9 (17.0)	49.7 (16.6)
Age categories [n (%)]			
>=85	1756 (0.8)	637 (0.8)	1119 (0.8)
75-84	13626 (6.3)	4058 (4.8)	9568 (7.2)
65-74	25019 (11.6)	7267 (8.6)	17752 (13.5)
55-64	27438 (12.7)	8787 (10.4)	18651 (14.1)
45-54	44252 (20.4)	15520 (18.4)	28732 (21.8)
35-44	46692 (21.6)	18115 (21.4)	28577 (21.7)
25-34	36338 (16.8)	17740 (21.0)	18598 (14.1)
18-24	21436 (9.9)	12453 (14.7)	8983 (6.8)
Sex [n (%)]			
Male	82,414 (38.1)	30683 (36.3)	51731 (39.2)
Female	134,143 (61.9)	53894 (63.7)	80249 (60.8)
Depression diagnosis at index visit [n (%)]			
Major depression			
Minor depression	78296 (36.2)	27029 (32.0)	51267 (38.8)

	138261 (63.8)	57548 (68.0)	80713 (61.2)
Baseline physical illnesses [n (%)]			
Cardiovascular disease	58350 (26.9)	18132 (21.4)	40218 (30.5)
Diabetes mellitus	23563 (10.9)	7198 (8.5)	16365 (12.4)
Chronic obstructive pulmonary disease	32898 (15.2)	10886 (12.9)	22012 (16.7)
Hyperlipidemia	23249 (10.7)	7351 (8.7)	15898 (12.0)
Hypertension	51271 (23.7)	15596 (18.4)	35675 (27.0)
Renal disease	11854 (5.5)	3766 (4.5)	8088 (6.1)
Cancer	8864 (4.1)	2850 (3.4)	6014 (4.6)
Baseline painful physical symptoms [n (%)]			
Musculoskeletal	99,455 (45.9)	36168 (42.8)	63287 (48.0)
Back	69,981 (32.3)	25036 (29.6)	44945 (34.1)
Gastrointestinal	111,271 (51.4)	40018 (47.3)	71253 (54.0)
Headache/migraine/dizziness	88,164 (40.7)	29996 (35.5)	58168 (44.1)
Baseline mental illnesses [n (%)]			
Schizophrenia	8207 (3.8)	1538 (1.8)	6669 (5.1)
Other psychotic disorder	4650 (2.1)	775 (0.9)	3875 (2.9)
Substance related	6127 (2.8)	1081 (1.3)	5046 (3.8)
Alcohol related	1748 (0.8)	254 (0.3)	1494 (1.1)
Drugs related	1084 (0.5)	196 (0.2)	888 (0.7)
Bipolar spectrum disorder	3882 (1.8)	457 (0.5)	3425 (2.6)
Dementia	7356 (3.4)	1426 (1.7)	5930 (4.5)

Generalized anxiety disorder	11718 (5.4)	2313 (2.7)	9405 (7.1)
Obsessive-compulsive disorder	3797 (1.8)	180 (0.2)	3617 (2.7)
Panic disorder	7388 (3.4)	588 (0.7)	6800 (5.2)
Phobic disorder	1742 (0.8)	131 (0.2)	1611 (1.2)
Post-traumatic stress disorder	404 (0.2)	20 (0.0)	384 (0.3)
Sleep disorder	52001 (24.0)	15196 (18.0)	36805 (27.9)
Hyperkinetic syndrome	133 (0.1)	22 (0.0)	111 (0.1)
Baseline healthcare service use			
Number of outpatient visits [mean (SD)]	31.6 (24.8)	23.9 (20.9)	36.5 (25.8)
	74970 (34.6)	26178 (31.0)	48792 (37.0)
ER visit [n (%)]	45397 (21.0)	13576 (16.1)	31821 (24.1)
Hospitalization [n (%)]			
Total 12-month costs prior to index date [mean (SD)]	1365.6 (2397.2)	894.6 (2089.0)	1667.5 (2529.6)
Index AD [n (%)]			
SSRI	98791 (45.6)	42476 (50.2)	56315 (42.7)
SNRI	18520 (8.6)	7549 (8.9)	10971 (8.3)
Other newer AD	6759 (3.1)	3104 (3.7)	3655 (2.8)
TCA	18787 (8.7)	5873 (6.9)	12914 (9.8)
Flupentixol/melitracen	11449 (5.3)	4341 (5.1)	7108 (5.4)
Other older AD	40897 (18.9)	14016 (16.6)	26881 (20.4)
Multiple AD	21354 (9.9)	7218 (8.5)	14136 (10.7)

Baseline characteristics were measured over the 12-month pre-index period.

Costs were expressed in 2003-4 US dollars.

SD=standard deviation; AD=antidepressant; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

*All comparisons between newly-diagnosed and non-newly-diagnosed depression were statistically significant with a p< 0.001 (chi-squared test was used for categorical variables and independent t-test for continuous variables).

Table 2. Service use and healthcare costs over the 12-month study period, overall sample

	Service use	
	n (% using)	mean (SD)
Psychiatric outpatient	184271 (85.1)	7.30 (7.72)
Psychiatric inpatient	10916 (5.0)	0.08 (0.46)
Psychiatric emergency	3515 (1.6)	0.03 (0.42)
Non-psychiatric outpatient	212327 (98.0)	27.48 (25.51)
Non-psychiatric inpatient	39077 (18.0)	0.33 (0.98)
Non-psychiatric emergency	70812 (32.7)	0.76 (3.13)
Healthcare costs ($, year 2003-4 values)		
		mean (SD)

Psychiatric outpatient	356.64 (465.87)
Psychiatric inpatient	148.22 (992.87)
Psychiatric emergency	0.86 (9.84)
Non-psychiatric outpatient	744.02 (1927.52)
Non-psychiatric inpatient	437.02 (2423.54)
Non-psychiatric emergency	44.46 (171.97)
Total	1731.21 (3508.72)

Table 3. Multivariate analysis (GLM) of total healthcare costs over the 12-month study period

	RR (95% CI)	
	The overall sample (n=216,557)	Newly-diagnosed depression (n=84,577)
Age	1.011 (1.011, 1.011)	1.013 (1.013, 1.014)
Sex		
Male	1.143 (1.134, 1.152)	1.231 (1.215, 1.247)
Female	1	1
Depression diagnosis at index visit		
Major depression	1.134 (1.125, 1.143)	1.160 (1.144, 1.176)
Minor depression	1	1

Past treatment history		
Newly-diagnosed depression	0.959 (0.952, 0.967)	--
Non-newly-diagnosed depression with history of both AD treatment and depression diagnosis	1.136 (1.121, 1.151)	--
Non-newly-diagnosed depression with history of either AD treatment or depression diagnosis	1	--
Index AD treatment		
SNRI	1.160 (1.144, 1.176)	1.144 (1.118, 1.170)
Other newer AD	1.142 (1.118, 1.166)	1.152 (1.114, 1.192)
TCA	0.905 (0.893, 0.918)	0.895 (0.872, 0.918)
Other older AD	0.956 (0.946, 0.965)	0.978 (0.960, 0.996)
Flupentixol/melitracen	0.876 (0.862, 0.891)	0.902 (0.876, 0.929)
Use of multiple ADs	1.177 (1.162, 1.192)	1.217 (1.189, 1.246)
SSRI	1	1
Baseline physical illnesses		
Cardiovascular disease		
Yes vs. No	1.180 (1.169, 1.191)	1.270 (1.248, 1.293)
Diabetes mellitus		
Yes vs. No	1.256 (1.240, 1.271)	1.315 (1.284, 1.347)
Chronic obstructive pulmonary disease		
Yes vs. No	1.122 (1.111, 1.134)	1.126 (1.104, 1.148)

Renal disease			
	Yes vs. No	1.161 (1.142, 1.181)	1.230 (1.190, 1.270)
Cancer			
	Yes vs. No	1.326 (1.302, 1.351)	1.478 (1.426, 1.532)
Baseline painful physical symptoms			
Musculoskeletal			
	Yes vs. No	1.068 (1.060, 1.077)	1.069 (1.054, 1.084)
Back			
	Yes vs. No	1.062 (1.053, 1.071)	1.069 (1.053, 1.085)
Gastrointestinal			
	Yes vs. No	1.067 (1.059, 1.075)	1.059 (1.045, 1.073)
Headache/migraine/dizziness			
	Yes vs. No	1.049 (1.040, 1.057)	1.046 (1.032, 1.061)
Baseline mental illnesses			
Schizophrenia			
	Yes vs. No	1.890 (1.854, 1.927)	2.456 (2.342, 2.575)
Other psychotic disorder			
	Yes vs. No	1.185 (1.156, 1.215)	1.368 (1.281, 1.461)
Substance related			
	Yes vs. No	1.301 (1.271, 1.331)	1.323 (1.249, 1.401)
Alcohol related			
	Yes vs. No	1.484 (1.423, 1.548)	1.662 (1.480, 1.867)
Drugs related			

	Yes vs. No	1.188 (1.128, 1.251)	1.483 (1.301, 1.690)
Bipolar spectrum disorder			
	Yes vs. No	1.233 (1.199, 1.267)	1.301 (1.194, 1.417)
Dementia			
	Yes vs. No	1.281 (1.255, 1.308)	1.355 (1.289, 1.424)
Generalized anxiety disorder			
	Yes vs. No	0.998 (0.982, 1.014)	0.996 (0.958, 1.035)
Obsessive-compulsive disorder			
	Yes vs. No	1.069 (1.039, 1.099)	0.978 (0.854, 1.120)
Panic disorder			
	Yes vs. No	0.961 (0.941, 0.980)	1.040 (0.964, 1.121)
Post-traumatic stress disorder			
	Yes vs. No	1.190 (1.094, 1.293)	0.983 (0.655, 1.476)
Total 12-month costs prior to index date (1000 USD)		1.182 (1.179, 1.185)	1.175 (1.170, 1.181)

RR=relative risk; CI=confidence interval; AD=antidepressant; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

Table 4. Multivariate analysis (GLM) of non-psychiatric costs and psychiatric costs over the 12-month study period, overall sample

	RR (95% CI)	
	Non-psychiatric healthcare costs	Psychiatric healthcare costs
Age	1.019 (1.019, 1.020)	0.998 (0.997, 0.998)

Sex		
Male	1.073 (1.063, 1.082)	1.214 (1.201, 1.226)
Female	1	1
Depression diagnosis at index visit		
Major depression	0.978 (0.969, 0.987)	1.363 (1.349, 1.377)
Minor depression	1	1
Past treatment history		
Newly-diagnosed depression	1.110 (1.100, 1.121)	0.696 (0.689, 0.704)
Non-newly-diagnosed depression with history of both AD treatment and depression diagnosis	1.076 (1.060, 1.093)	1.359 (1.334, 1.385)
Non-newly-diagnosed depression with history of either AD treatment or depression diagnosis	1	1
Index AD treatment		
SNRI	0.995 (0.979, 1.011)	1.396 (1.372, 1.421)
Other newer AD	1.014 (0.988, 1.040)	1.323 (1.288, 1.360)
TCA	1.046 (1.029, 1.063)	0.709 (0.695, 0.723)
Other older AD	1.063 (1.051, 1.076)	0.841 (0.829, 0.853)
Flupentixol/melitracen	1.031 (1.011, 1.052)	0.681 (0.664, 0.699)
Use of multiple ADs	1.070 (1.054, 1.086)	1.434 (1.409, 1.458)
SSRI	1	1
Baseline physical illnesses		

Cardiovascular disease			
	Yes vs. No	1.252 (1.238, 1.266)	1.015 (1.002, 1.029)
Diabetes mellitus			
	Yes vs. No	1.362 (1.343, 1.382)	0.991 (0.974, 1.009)
Chronic obstructive pulmonary disease			
	Yes vs. No	1.168 (1.153, 1.182)	1.004 (0.990, 1.019)
Renal disease			
	Yes vs. No	1.245 (1.220, 1.270)	0.855 (0.835, 0.876)
Cancer			
	Yes vs. No	1.562 (1.528, 1.597)	0.857 (0.835, 0.880)
Baseline painful physical symptoms			
Musculoskeletal			
	Yes vs. No	1.132 (1.121, 1.143)	0.974 (0.963, 0.984)
Back			
	Yes vs. No	1.120 (1.109, 1.131)	0.971 (0.960, 0.982)
Gastrointestinal			
	Yes vs. No	1.163 (1.153, 1.174)	0.955 (0.945, 0.965)
Headache/migraine/dizziness			
	Yes vs. No	1.088 (1.078, 1.098)	1.033 (1.022, 1.044)

Baseline mental illnesses			
Schizophrenia			
	Yes vs. No	0.892 (0.871, 0.931)	3.443 (3.358, 3.531)
Other psychotic disorder			
	Yes vs. No	0.966 (0.937, 0.996)	1.514 (1.465, 1.565)
Substance related			
	Yes vs. No	1.335 (1.298, 1.372)	1.323 (1.282, 1.364)
Alcohol related			
	Yes vs. No	1.467 (1.395, 1.544)	1.707 (1.614, 1.805)
Drugs related			
	Yes vs. No	1.196 (1.124, 1.273)	1.208 (1.129, 1.292)
Bipolar spectrum disorder			
	Yes vs. No	0.991 (0.958, 1.024)	1.649 (1.590, 1.709)
Dementia			
	Yes vs. No	1.291 (1.260, 1.323)	1.451 (1.407, 1.496)
Generalized anxiety disorder			
	Yes vs. No	1.007 (0.988, 1.026)	1.016 (0.994, 1.038)
Obsessive-compulsive disorder			
	Yes vs. No	0.837 (0.809, 0.865)	1.241 (1.197, 1.286)
Panic disorder			
	Yes vs. No	0.902 (0.881, 0.924)	1.062 (1.034, 1.090)
Post-traumatic stress disorder			
	Yes vs. No	1.045 (0.946, 1.154)	1.229 (1.104, 1.368)

Total 12-month costs prior to index date (1000 USD)	1.200 (1.197, 1.203)	1.078 (1.074, 1.082)

RR=relative risk; CI=confidence interval; AD=antidepressant; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

Table 5. Multivariate logistic analysis for use of psychiatric inpatient and emergency services over the 12-month study period, overall sample

	OR (95% CI)	
	Use of psychiatric inpatient services	Use of psychiatric emergency services
Age	0.974 (0.972, 0.975)	0.949 (0.947, 0.952)
Sex		
Male	1.689 (1.620, 1.762)	1.731 (1.613, 1.858)
Female	1	1
Depression diagnosis at index visit		
Major depression	1.909 (1.830, 1.991)	1.771 (1.650, 1.901)
Minor depression	1	1
Past treatment history		
Newly-diagnosed depression	1.093 (1.042, 1.147)	1.022 (0.943, 1.108)
Non-newly-diagnosed depression with history of both AD treatment and depression diagnosis	2.445 (2.310, 2.588)	1.593 (1.441, 1.762)
Non-newly-diagnosed depression with history of	1	1

either AD treatment or depression diagnosis			
Index AD treatment			
	SNRI	1.385 (1.295, 1.481)	0.736 (0.642, 0.843)
	Other newer AD	1.712 (1.558, 1.880)	1.007 (0.838, 1.209)
	TCA	0.747 (0.680, 0.820)	0.831 (0.708, 0.974)
	Other older AD	0.926 (0.872, 0.984)	1.169 (1.062, 1.287)
	Flupentixol/melitracen	0.601 (0.525, 0.688)	1.300 (1.097, 1.540)
	Use of multiple ADs	1.454 (1.365, 1.549)	1.388 (1.250, 1.543)
	SSRI	1	1
Baseline physical illnesses			
Cardiovascular disease			
	Yes vs. No	1.060 (1.003, 1.120)	1.292 (1.178, 1.417)
Chronic obstructive pulmonary disease			
	Yes vs. No	1.080 (1.017, 1.147)	1.120 (1.010, 1.241)
Renal disease			
	Yes vs. No	0.741 (0.667, 0.824)	--
Cancer			
	Yes vs. No	0.773 (0.685, 0.873)	--
Baseline painful physical symptoms			

Headache/migraine/dizziness			
		1.062 (1.016, 1.109)	1.125 (1.046, 1.211)
	Yes vs. No		
Baseline mental illnesses			
Schizophrenia			
	Yes vs. No	4.271 (4.010, 4.548)	2.971 (2.688, 3.283)
Other psychotic disorder			
	Yes vs. No	1.776 (1.616, 1.953)	1.594 (1.374, 1.848)
Substance related			
	Yes vs. No	2.277 (2.099, 2.471)	1.982 (1.742, 2.255)
Alcohol related			
	Yes vs. No	3.526 (3.112, 3.995)	2.014 (1.656, 2.449)
Drugs related			
	Yes vs. No	1.257 (1.051, 1.502)	1.328 (1.038, 1.699)
Bipolar spectrum disorder			
	Yes vs. No	2.453 (2.236, 2.691)	2.655 (2.321, 3.037)
Dementia			
	Yes vs. No	1.817 (1.638, 2.015)	1.440 (1.172, 1.770)
Generalized anxiety disorder			
	Yes vs. No	0.840 (0.759, 0.929)	--
Obsessive-compulsive disorder			
	Yes vs. No	0.864 (0.757, 0.987)	1.278 (1.068, 1.529)
Panic disorder			

	Yes vs. No	0.825 (0.736, 0.924)	1.478 (1.271, 1.718)
Total 12-month costs prior to index date (1000 USD)		1.059 (1.052, 1.067)	1.033 (1.021, 1.045)

OR=odds ratio; CI=confidence interval; AD=antidepressant; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; other newer AD: bupropion and mirtazapine; other older AD: maprotiline, moclobemide, and trazodone.

Formatted: Font: (Default) Times New Roman, Font color: Black