Beyond Symptomatic Improvement: Assessing Real-World Outcomes in Patients With Major Depressive Disorder

Alan M. Langlieb, MD, MPH, MBA,
and Christine J. Guico-Pabia, MD, MPH, MBA

Objective: To quantify the negative impact that major depressive disorder (MDD) has on quality of life, disability, and work, family, and overall psychosocial functioning. Available scales that assess these areas of impairment as they relate to patients with MDD are described.

Data Sources: PubMed searches were conducted using the following terms: (*MDD* OR *major depressive disorder*) AND (*absenteeism* OR *absente**); AND (*quality of life* OR *QOL*); AND (*psychosocial function**); AND (*presente** OR *presenteeism*); AND (*health care cost** OR *[health care] cost**); AND (*health outcome**); AND (*functional outcome**); AND (*family life*); AND (*disabil** OR *disability*); AND (*work function**); AND (*unemployment* OR *unemploy**). The literature search was conducted in July 2008 and was restricted to English language articles. There were no limits set on the dates of the search.

Study Selection: Two hundred twenty potential articles were identified. Among these studies, 48 presented primary data directly demonstrating the effect of MDD on quality of life, disability, and work, family, and overall psychosocial functioning.

Data Extraction: Primary data were compiled from these studies and are summarily described. Available scales that assess quality of life, disability, and work, family, and overall psychosocial functioning are also described.

Data Synthesis: MDD was found to be associated with significant disability and declines in functioning and quality of life. The Sheehan Disability Scale, the 36-item Short-Form Health Survey, and the Work Limitations Questionnaire were the most commonly used scales according to this review of the literature, but the majority of studies used direct and indirect disability measures, such as health care and other disability-related costs.

Conclusions: In addition to assessing symptomatic outcomes, physicians should routinely assess their depressed patients on "real-world" outcomes. The development of a concise functional outcome measure specific to MDD is necessary for busy clinical practices.

Prim Care Companion J Clin Psychiatry 2010;12(2):e1–e14

© Copyright 2010 Physicians Postgraduate Press, Inc.

Submitted: *April 14, 2009; accepted August 4, 2009.*
Published online: *April 15, 2010 (doi:10.4088/PCC.09r00826blu).*
Corresponding author: *Alan M. Langlieb, MD, The Johns Hopkins Bloomberg School of Public Health, 624 N Broadway, Baltimore, MD 21205 (drlanglieb@gmail.com).*

According to the National Comorbidity Survey (NCS), major depressive disorder (MDD) has an estimated lifetime prevalence of 16%. NCS data also reveal that the majority of participants that met MDD criteria were currently employed and during the past year experienced some form of role impairment in work, family, or social functioning. The degree of impairment was commensurate with the severity of depressive symptomatology.[1] Furthermore, the World Health Organization has estimated that, among the 10 most disabling diseases (eg, diabetes, tuberculosis, hepatitis, sexually transmitted diseases), MDD is responsible for 5% of the total global disease burden associated with these disorders[2] and is ranked fourth among the leading causes of disease burden.[3]

Despite the overwhelming evidence demonstrating that MDD exerts a significantly negative effect on functioning and quality of life (Table 1), when depressed patients are assessed, either in a clinical or research setting, the focus primarily remains on the severity of depressive symptoms, with significantly less attention being paid to the impact that MDD has on these "real-world" outcomes. Other areas of medicine (eg, cardiovascular medicine,[4,5] diabetes[6]) have begun to expand the assessment of treatment outcomes from simply measuring symptomatic improvement to include a broader range of outcomes, thereby providing a useful example of how assessing these outcomes can help in the decision-making process of the various health care stakeholders (ie, physicians, employers, and payors/managed care plans) involved in the treatment of depressed patients.

The objective of this systematic review was to quantify the negative impact that MDD has on quality of life, disability, and work, family, and overall psychosocial functioning. Available scales that assess these areas of impairment as they relate to patients with MDD are also described.

METHOD

PubMed searches were conducted using the following terms: (*MDD* OR *major depressive disorder*) AND (*absenteeism* OR *absente**); AND (*quality of life* OR *QOL*); AND (*psychosocial function**); AND (*presente**

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

Clinical Points

- Major depressive disorder is associated with significant declines in functioning and quality of life.
- In addition to measuring the severity of depressive symptoms, clinicians and researchers should assess depressed patients' level of functioning and quality of life.
- A number of scales are currently available that are valid and reliable measures of functioning and quality of life.

OR *presenteeism*); AND (*health care cost** OR *[health care] cost**); AND (*health outcome**); AND (*functional outcome**); AND (*family life*); AND (*disabil** OR *disability*); AND (*work function**); AND (*unemployment* OR *unemploy**). The literature search was conducted in July 2008 and was restricted to English language articles. There were no limits set on the dates of the search.

Two hundred twenty potential articles were identified. Among these studies, 48 presented primary data directly demonstrating the effect of MDD on these outcomes. Primary data were compiled from these studies and are summarily described. Available scales that assess these outcomes are also described.

COSTS ASSOCIATED WITH MDD

The substantial direct and indirect health care costs associated with depression alone[7–9] and comorbid with other conditions[10–13] have been quantified by a number of large-scale evaluations. Correspondingly, depression also has been shown to negatively impact an individual's overall health and can lead to increased costs for treating any co-occurring disorders. For instance, in 2 studies that assessed diabetic patients with and without comorbid depression, significantly higher health care costs[14] and worse clinical outcomes, including higher mortality rates,[15] were observed in those with a co-occurring depressive disorder.

In a large-scale assessment of employees of a major corporation,[10] the per-capita health and disability costs (including direct health care expenditures and sick/disability days) associated with depression were $5,415 annually, equivalent to diabetes ($5,472), heart disease ($5,523), and back problems ($4,388), but significantly greater than hypertension ($3,372; $P = .002$) and a category containing "all other" reasons for filing a health claim ($1,292; $P < .001$). In addition, when MDD co-occurred with one of these general medical conditions, the associated health care costs increased nearly 2-fold compared to patients with the medical disorder alone. The resulting cost to the corporation was $2.2 million.[10,11] In addition, other studies have demonstrated a significant association between MDD, cardiac death,[16,17] and total mortality.[16] Beyond medical comorbidities, MDD is also commonly comorbid with other psychiatric disorders. In particular, MDD commonly co-occurs with generalized anxiety disorder, which results in significant disability.[18]

IMPAIRED FUNCTIONING AND QUALITY OF LIFE ASSOCIATED WITH MDD

The terms *functioning* and *quality of life* are often used interchangeably; however, the disability associated with each and the means in which they are assessed are multidimensional and can differ significantly. Assessments of functioning generally include performance-based metrics, such as one's ability to engage in expected or usual responsibilities at work or home, and can be assessed using objective measures, such as days of work missed, or subjectively, using patient-rated assessments. However, functioning does not distinctly involve work performance; functioning in other areas, such as in familial, societal, and marital roles, also can be adversely affected by MDD. Quality-of-life measures, on the other hand, generally describe the subjective quality of an individual's day-to-day experiences, which involve enjoyment and satisfaction with one's life, but also can be related to the patient's performance in his or her expected role.

Work Functioning

A number of studies have empirically demonstrated that MDD not only negatively impacts those who are currently employed[19–22] but also is associated with an increased risk for job loss.[23] One large-scale analysis of NCS data suggested that those in the middle of their careers are more likely than their younger counterparts to lose their jobs as the result of a major depressive episode.[24] The most obvious way that MDD impacts work performance is the elevated rates of absenteeism among depressed employees.[9,10] However, the negative effect that MDD has on work performance extends beyond whether an employee is present to perform his or her job.

Presenteeism describes the impaired functioning that employees experience when they attend work but suboptimally perform their daily activities, in this case, due to their depressive symptoms. Depressed employees have been shown to be particularly prone to detriments in

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1. Summary of Key Studies Assessing the Disability Associated With Major Depressive Disorder (MDD)

Reference	Study Description	Primary Results
Arnow et al, 2006[95]	Patients with and without MDD and chronic pain were evaluated with the SF-8 to assess the impact of MDD on health-related quality of life	MDD/disabling pain: 31.3; $P < .0001$ vs all groups MDD/nondisabling pain: 27.9; $P < .0001$ vs controls MDD alone: 26.7; $P < .0001$ vs controls Neither MDD nor pain: 16.8
Barefoot et al, 1996[16]	Patients with coronary artery disease with and without depression (n = 1,250) were followed for a median of 15 y	Risk of cardiac death $\chi^2_1 = 9.25$; $P = .002$ vs nondepressed patients Total mortality $\chi^2_1 = 14.67$; $P < .001$ vs nondepressed patients 51% of moderate-to-severe depression group died of cardiac causes
Baune et al, 2007[44]	Patients with common medical disorders with and without comorbid MDD were assessed to determine the impact of MDD on functioning and health outcomes	Risk of experiencing disability days (mean risk vs those without comorbid MDD) Overall: 1.34; $P = .012$ Neurologic: 2.62; $P = .0005$ Gastrointestinal: 1.38; $P = .079$ Cardiovascular: 1.16; $P = .359$ Endocrine: 1.70; $P = .047$ Allergic: 1.06; $P = .399$ Respiratory: 2.02; $P = .069$
Beekman et al, 2002[45]	Adults aged 55–85 y (n = 2,200) were followed for 3 y to determine the impact of MDD on use of health services	Risk associated with the onset of MDD, OR (95% CI) Disability days: 2.10 (1.38–3.20) Hospital admission: 1.80 (1.15–2.81) Use of paramedical services: 1.88 (1.15–3.08) Impaired general satisfaction: 4.11 (2.65–6.38) Risk associated with persistent MDD, OR (95% CI) Fewer physician visits: 0.38 (0.19–0.75) Impaired general satisfaction: 3.73 (2.04–6.83) Dissatisfaction with services: 3.08 (1.39–6.83)
Birnbaum et al, 2003[8]	The disability costs associated with depression were analyzed by gender	Total costs Males with MDD: $8,502 (work absence: 42%; prescription drugs: 11%; medical: 48%) Males without MDD: $3,458 (work absence: 39%; prescription drugs: 13%; medical: 47%) Females with MDD: $9,265 (work absence: 50%; prescription drugs: 11%; medical: 40%) Females without MDD: $5,091 (work absence: 53%; prescription drugs: 11%; medical: 36%)
Breslau et al, 2003[96]	Patients with migraines, patients with severe headaches, and nonheadache controls were followed for 2 y to assess the relationship between MDD and headaches	Risk for migraine, OR (95% CI) Controls with MDD: 3.4 (1.4–8.7); $P < .01$ vs controls without MDD Risk for MDD, OR (95% CI) Migraine without MDD: 5.8 (2.7–12.3); $P < .0001$ vs controls without headache or MDD
Breslin et al, 2006[97]	Adults aged 18–60 y were followed for 4 y and assessed to determine the effect of MDD on activity limitation	Risk for activity limitation associated with MDD, OR Home Female: 3.8 Male: 4.2 Work Female: 3.4 Male: 3.4 Other Female: 3.5 Male: 5.7
Burton et al, 2004[98]	Depressed employees (n = 1,491) from a large financial services company were assessed with the WLQ	Risk for low score on WLQ scales, OR (95% CI) Time: 2.05 (1.83–2.30); $P < .05$ Physical: 1.49 (1.32–1.68); $P < .05$ Mental: 2.46 (2.20–2.76); $P < .05$ Output: 2.24 (2.00–2.50); $P < .05$

(continued)

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1 (continued). Summary of Key Studies Assessing the Disability Associated With Major Depressive Disorder (MDD)

Reference	Study Description	Primary Results
Carta et al, 2003[99]	Direct health care costs of patients with depression, patients with a chronic somatic illness, and healthy controls were compared	Hospital days, mean Depressed: 5.8 d ($P<.0001$ vs somatic and healthy) Antidepressant treatment: 2.0 d ($P<.04$ vs no antidepressant treatment) No antidepressant treatment: 7.4 d Somatic: 4.3 d Healthy: 1.1 d Daily drug expenditures, mean Depressed: €0.53 ($P<.0001$ vs somatic and healthy) Antidepressant treatment: €0.65 ($P=.28$ vs no antidepressant treatment) No antidepressant treatment: €0.51 Somatic: €0.52 Healthy: €0.21 Drug and hospitalization expenditures during previous year Depressed: €2,289.41 ($P<.0001$ vs somatic and healthy) Antidepressant treatment: €1,715.81 ($P<.04$ vs no antidepressant treatment) No antidepressant treatment: €2,528.40 Somatic: €1,750.37 Healthy: €474.11
Cramer et al, 2003[100]	Epilepsy patients with mild-moderate (n = 74) or severe (n = 166) depression and those without depression (n = 443) were assessed with a seizure severity scale	Patients with mild-moderate and severe depression experienced more severe, bothersome, and frequent seizures that were more difficult to recover from than nondepressed patients
Dorenlot et al, 2005[46]	Dementia outpatients were followed for 3 y to assess the impact of MDD on rates of institutionalization	Risk for institutionalization, OR (95% CI) MDD: 1.6 (1.1–2.5); $P=.043$ vs non-MDD controls
Druss et al, 2000[10]	Employees (n = 15,153) of a large US corporation who filed health claims were assessed on health care and disability costs	Depressive disorder (MDD, dysthymia, depressive disorder not otherwise specified) Sick days: 9.9; $P<.05$ vs diabetes, heart disease, hypertension, back problems, all other Per capita health/disability costs: $5,415; $P<.01$ vs hypertension, all other Diabetes, heart disease, hypertension, or back problem with comorbid depressive disorder Health care costs: $7,407; $P<.001$ vs any disorder without comorbid depressive disorder Sick days: 13.5; $P<.01$ vs any disorder without comorbid depressive disorder Per capita health care costs: $7,906; $P<.001$ vs any disorder without comorbid depressive disorder
Druss et al, 1999[101]	Health care costs of patients with MDD (n = 1,081) were compared with nondepressed controls	Increase in outpatient care costs: $1,326; $P<.001$ vs nondepressed controls Increase in inpatient care costs: $1,581; $P<.001$ vs nondepressed controls
Egede et al, 2004[102]	Patients with MDD and diabetes, MDD without diabetes, and diabetes only and nondepressed, nondiabetic controls were assessed on their physical functioning	Prevalence of overall functional disability MDD/diabetes: 77.8%; $P<.0001$ vs controls Diabetes only: 58.1%; $P<.0001$ vs controls MDD only: 51.3%; $P<.0001$ vs controls No MDD/no diabetes: 24.5%; $P<.0001$ vs controls Risk of functional disability, OR (95% CI) MDD: 3.02 (2.66–3.44) Diabetes: 2.46 (2.15–2.82) MDD and diabetes: 6.15 (3.86–9.80)
Egede, 2007[47]	The 12-mo prevalence of MDD in patients with a number of CMDs was assessed to determine the effect of MDD on health care utilization	Risk, OR (95% CI) ≥ 1 day absent from work CMD: 0.98 (0.80–1.21) CMD/MDD: 1.22 (0.88–1.68) ≥ 1 day spent in bed CMD: 0.97 (0.85–1.10) CMD/MDD: 1.60 (1.28–2.00) Functional disability: yes CMD: 1.06 (0.91–1.24) CMD/MDD: 2.48 (1.96–3.15)
Ford et al, 2004[103]	The effect of depression on health care utilization was assessed	Patients with depression are significantly more likely to be high (14%; OR [95% CI]: 2.2 [1.2–3.9]) vs midrange (7%) health care utilizers

(continued)

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1 (continued). Summary of Key Studies Assessing the Disability Associated With Major Depressive Disorder (MDD)

Reference	Study Description	Primary Results
Frasure-Smith et al, 1993[104]	Patients who met criteria for a myocardial infarction and screened positively for MDD (n = 35) were followed for 6 mo to compare mortality rates with nondepressed controls (n = 187)	Risk for mortality, OR (95% CI) 5.74 (4.61–6.87); $P < .0006$ vs nondepressed controls
Greenberg et al, 2003[7]	The economic burden of depression for the year 2000 was calculated from a variety of sources presenting US data	Inpatient: $8,883 (million) Outpatient: $6,083 (million) Pharmaceutical: $10,400 (million) Absenteeism: $36,248 (million) Presenteeism: $15,195 (million)
Haarasilta et al, 2005[105]	Adolescents and young adults (n = 942) were followed for 1 y to assess the relationship between MDD and health	Risk of poor health, OR (95% CI) Chronic illness: 1.59 (0.93–2.70) Diagnosed chronic illness: 1.76 (1.03–3.01) Respiratory allergies: 2.71 (1.14–6.45) Other allergies: 1.31 (0.65–2.66) Musculoskeletal: 1.51 (0.60–3.79) Neurologic: 1.85 (0.53–6.45) Migraine: 3.67 (0.96–14.0) Disabling chronic illness: 1.35 (0.55–3.31) Poor self-perceived health: 2.56 (1.23–5.34) ≥ 3 sick days: 2.01 (1.23–3.29)
Hoge et al, 2002[106]	Health care utilization of active military personnel between 1990 and 1999 was calculated to identify the effect that a psychiatric diagnosis has on this metric	MDD (1990–1999) Hospitalizations: 11,264 Ambulatory visits: 100,866
Janssens et al, 2003[107]	Patients with multiple sclerosis (n = 101) were screened for depression to assess its relationship to SF-36 scores	SF-36 physical health Physical functioning: $\beta = -.45$; $P < .001$ Role-physical functioning: $\beta = -.53$; $P < .001$ Bodily pain: $\beta = -.43$; $P < .001$ General health: $\beta = -.41$; $P < .001$ SF-36 mental health Vitality: $\beta = -.51$; $P < .001$ Social functioning: $\beta = -.57$; $P < .001$ Role-emotional functioning: $\beta = -.45$; $P < .001$ Mental health: $\beta = -.64$; $P < .001$
Katon et al, 2003[13]	The medical costs of older adults diagnosed with MDD were compared with nondepressed controls	Cost ratios associated with MDD, OR (95% CI) Total: 1.49 (1.28–1.72) Total outpatient: 1.47 (1.36–1.56) Outpatient depression: 1.78 (1.42–2.24) Outpatient nondepression: 1.36 (1.18–1.56)
Kaufmann et al, 1999[17]	Patients with myocardial infarction (n = 331) were followed for 12 mo to assess the effect of MDD (27%) on mortality in these patients	Mortality MDD: 18.7%; OR = 2.33 (95% CI = 1.16–4.65); $P = .015$ Non-MDD: 9.0%
Keenan-Miller et al, 2007[108]	Adolescents were followed for 5 y to assess the effect of MDD on health outcomes in young adulthood	MDD at age 15 y, β (95% CI) Interviewer-rated health: .16 (0.04–0.29); $P = .01$ SF-36 self-rated health: 1.10 (0.17–2.02); $P = .02$ SF-36 physical limitations: .62 (−0.22–1.45); $P = .15$ Visit to medical professional: 1.26 (0.61–1.90); $P = .001$ SF-36 work role impairment: .38 (0.15–0.60); $P = .001$ Chronic illness at age 20 y, OR (95% CI): 1.62 (0.98–2.67); $P = .06$
Kessler et al, 1999[109]	Work disability data from 2 nationally representative populations were assessed to quantify the effect of 30 d of experiencing MDD	Short-term work disability: 45.9% ($P < .05$ vs non-MDD workers) Work disability days: 7.6 ($P < .05$ vs non-MDD workers) Salary-equivalent disability costs: $267
Kessler et al, 2003[110]	The disability data from a nationally representative sample diagnosed with hypertension, arthritis, asthma, and ulcer with MDD were compared	Difference in number of role impairment days Hypertension: 1.6 (P = NS vs no comorbid MDD) Arthritis: 2.2 (P = NS vs no comorbid MDD) Asthma: 2.4 ($P < .05$ vs no comorbid MDD) Ulcer: 3.1 ($P < .05$ vs no comorbid MDD)
Kessler et al, 2006[9]	Using NCS data, an analysis of performance was conducted in workers with MDD	Aggregated (total US population) impact of MDD Absenteeism Days per year (million): 72.2; $P < .05$ Dollars per year (million): 11,742; $P < .05$ Presenteeism Days per year (million): 150.5; $P < .05$ Dollars per year (million): 24,482; $P < .05$ Total Days per year (million): 225.0; $P < .05$ Dollars per year (million): 36,602; $P < .05$

(continued)

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1 (continued). Summary of Key Studies Assessing the Disability Associated With Major Depressive Disorder (MDD)

Reference	Study Description	Primary Results
Kouzis and Eaton, 1994[111]	The predictors of emotional disability days were assessed	Disability associated with MDD ≥1 disability day: 44% Risk for disability day: OR = 27.8 (95% CI = 6.93–108.96)
Lerner et al, 2004[23]	Work outcomes in employees with MDD (n = 75) were compared with healthy controls (n = 169) over 6 mo	WLQ scales (change from baseline to 6 mo) Physical MDD: −3.3; *P* = NS Controls: −0.8 Time MDD: −3.9; *P* = .014 Controls: −0.2 Mental MDD: −9.4; *P* < .001 Controls: −1.4 Output MDD: −12.0; *P* < .001 Controls: −1.4
Lerner et al, 2004[112]	The effect of MDD on work productivity outcomes was assessed with the WLQ	WLQ scales Mental-interpersonal: β = 50.8; *P* < .001 Physical: β = 12.9; *P* = .004 Time: β = 46.4; *P* < .001 Output: β = 59.7; *P* < .001 Days missed: 2.2; *P* < .001
Lespérance et al, 2002[113]	The association between 5-y risk of cardiac mortality and BDI severity score was assessed in patients with myocardial infarction (n = 879)	Cardiac mortality, OR (95% CI) BDI score 5–9 vs < 5: 1.76 (0.98–3.17); *P* = .059 BDI score 10–18 vs < 5: 3.17 (1.79–5.60); *P* < .001 BDI score ≥ 19 vs < 5: 3.13 (1.56–6.27); *P* = .001
Luber et al, 2000[114]	The health care utilization of internal medicine outpatients with a diagnosis of MDD was compared to nondepressed controls over 1 y	Health care visits MDD: 5.3; *P* < .001 vs controls Controls: 2.9 Total health care costs MDD: $2,808; *P* = .001 vs controls Controls: $1,891
McIntyre et al, 2008[115]	The impact of MDD on work functioning was assessed in a large, nationally representative sample	Risk associated with MDD, OR (95% CI) ≥1 disability day in past 2 wk: 5.6 (4.1–7.7); *P* < .05 vs reference group Good job security: 0.7 (0.6–0.8); *P* < .05 vs reference group
McQuaid et al, 1999[116]	A population of primary care patients was used to assess the impact of MDD on work functioning	Missed work days MDD: 58.1% ($\chi^2_1 = 15.10$; *P* < .001) No MDD: 28.7% Cut down on activities MDD: 77.0% ($\chi^2_1 = 9.03$; *P* < .01) No MDD: 54.3%
Muchmore et al, 2003[117]	A predictor analysis was conducted in arthritis patients to assess the impact of arthritis and associated conditions, including MDD, on disability	Risk associated with comorbid depression, OR (95% CI) Short-term disability: 1.01 (1.00–1.02); *P* < .0001 Long-term disability: 2.23 (1.49–3.32); *P* < .0001 Worker's compensation: 1.45 (1.25–1.70); *P* < .0001
Papapetropoulos et al, 2006[48]	PD patients with and without MDD were assessed with PD rating scales	PD severity ratings Unified Parkinson's Disease Rating Scale, mean (SD)[118] PD/MDD: 58.1 (32.3); *P* = .004 PD: 37.3 (31.1) Hoehn and Yahr, mean (SD)[119] PD/MDD: 2.7 (1.0); *P* = .07 PD: 2.2 (0.9) Schwab and England, activities of daily living performed, % (SD)[120] PD/MDD: 69.4% (22.1); *P* = .03 PD: 78.4% (22.3)
Penninx et al, 2001[121]	Mortality rates of patients diagnosed with and without CD and with and without MDD (n = 2,847) were compared	CD mortality, OR (95% CI) No CD/MDD: 3.8 (1.4–10.6) CD/No MDD: 3.4 (2.4–4.9) CD/MDD: 10.5 (4.1–26.7) IHD mortality, OR (95% CI) No CD/MDD: 5.1 (1.6–16.9) CD/No MDD: 4.5 (2.8–7.1) CD/MDD: 17.7 (6.0–51.9)
Rovner, 1993[122]	Nursing home patients were followed for 1 y to determine the effects of MDD on mortality rates	Risk for mortality in MDD, OR (95% CI): 1.59 (1.02–2.51)

(continued)

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1 (continued). Summary of Key Studies Assessing the Disability Associated With Major Depressive Disorder (MDD)

Reference	Study Description	Primary Results
Rumsfeld et al, 2003[123]	Veterans' affairs patients with a history of acute coronary syndrome with MDD (n = 1,431) were compared with nondepressed controls (n = 526) on a variety of health and quality of life outcomes	MDD vs controls, OR (95% CI) Higher angina frequency: 2.40 (1.86–3.10); $P < .001$ Greater physical limitations: 2.89 (2.17–3.86); $P < .001$ Worse quality of life: 2.84 (2.16–3.72); $P < .001$
Saarijärvi et al, 2002[36]	SF-36 data from patients with MDD and nondepressed controls were compared to determine the impact of MDD on quality of life	Relationship between SF-36 and BDI in MDD patients Physical functioning ($P \leq .01$) Role functioning-physical ($P < .001$) Role functioning-emotional ($P < .01$) Energy ($P = .0001$) Emotional well-being ($P = .0001$) Social functioning ($P = .0001$) Bodily pain ($P = .0001$) General health perception ($P = .0001$)
Simon et al, 1995[124]	Primary care patients with and without depression were compared on health care costs over 1 y following diagnosis	Annual total direct health care costs (eg, outpatient and inpatient mental health care, outpatient primary care, inpatient medical) Depressed: $4,246 Not depressed: $2,371
Simon et al, 2000[49]	A 2-y follow-up of patients beginning antidepressant therapy assessed patients on a variety of work outcomes according to treatment response (ie, persistent [n = 35], improved [n = 137], or remitted [n = 118] depression)	Total health care costs Persistent: $4,082 Improved: $3,459 Remitted: $2,816 Employed, % ($F_{2,262} = 5.88$, $P = .003$) Persistent: 70.1 Improved: 83.8 Remitted: 85.4 Days of work missed ($F_{2,226} = 10.62$, $P < .001$) Persistent: 16.80 Improved: 10.37 Remitted: 6.29
Sobocki et al, 2006[125]	Direct and indirect health costs (in year 2004 € million) collected from published studies conducted in 28 European countries were calculated	Total costs: €117,851 Total direct costs: €41,688 Hospitalization costs: €10,424 Drug costs: €9,013 Outpatient care: €22,252 Total indirect costs: €76,163 Morbidity: €72,189 Mortality: €3,974
Spitzer et al, 1995[35]	Primary care patients diagnosed with MDD (n = 115) were compared with controls on the subscales of the SF-20 to assess the impact of MDD on health-related quality of life	MDD vs nonpsychiatrically diagnosed patients Physical functioning: –21.8; $P < .001$ Bodily pain: –22.7; $P < .001$ Role functioning: –45.5; $P < .001$ General health: –30.4; $P < .001$ Social functioning: –31.7; $P < .001$ Mental health: –36.5; $P < .001$
Stewart et al, 2003[28]	Depressed (n = 219) and nondepressed (n = 908) employees were compared on the cost of lost productive time	Lost productive time (hr/wk) Absenteeism: 1.2 Presenteeism: 7.2 Total lost productive time: 8.4 Cost of lost productive time ($ billion per year) Absenteeism: 3.18 Presenteeism: 18.18 Total lost productive time: 21.36
Sullivan et al, 1997[126]	The physical functioning of patients with coronary artery disease was compared by baseline $HDRS_{17}$ score and severity of depression over a 12-mo follow-up period	Relationship between functioning and baseline $HDRS_{17}$ score Physical function score at 12 mo: $r = –0.27$; $P < .001$ Activity interference at 12 mo: $r = 0.23$; $P < .01$ A significant association (ANOVA) between baseline depressive severity and physical functioning was observed at baseline ($P < .001$) and 12 mo ($P = .01$)

(continued)

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1 (continued). Summary of Key Studies Assessing the Disability Associated With Major Depressive Disorder (MDD)

Reference	Study Description	Primary Results
Sullivan et al, 2000[127]	The physical functioning of patients with coronary artery disease was compared by baseline $HDRS_{17}$ score and severity of depression over a 5-y follow-up period	Relationship between disability and $HDRS_{17}$ score SF-36 scales Physical function: $r = 0.26$; $P < .01$ Physical role: $r = 0.36$; $P < .001$ Pain: $r = 0.28$; $P < .01$ Social function: $r = 0.31$; $P < .001$ Mental health: $r = 0.21$; $P < .05$ Emotional role: $r = 0.21$; $P < .05$ Vitality: $r = 0.36$; $P < .0001$ General health: $r = 0.33$; $P < .0001$
Unützer et al, 1997[128]	A 4-y prospective study of Medicare enrollees ≥ 65 y who were screened for depression; health care costs were compared between those with depression (n = 353) and those without (n = 2,165)	Median costs 1 y after baseline Depressed: $2,147 Not depressed: $1,461 Median costs 4 y after baseline Depressed: $15,423 Not depressed: $10,152
Wells et al, 1989[30]	Data from 11,242 participants of the Medical Outcomes Study receiving treatment from general medical providers were subdivided into NCC and MDD groups	Physical functioning NCC: 85.4; $P < .05$ MDD: 81.3 Social functioning NCC: 91.7; $P < .0001$ MDD: 83.3 Role functioning NCC: 87.0; $P < .0001$ MDD: 74.6

Abbreviations: ANOVA = analysis of variance, BDI = Beck Depression Inventory, CD = cardiac disease, CMD = chronic medical disorder, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, IHD = ischemic heart disease, NCC = no chronic condition, NCS = National Comorbidity Survey, NS = not significant, OR = odds ratio, PD = Parkinson's disease, SF-8 = 8-item Short-Form Health Survey, SF-20 = 20-item Short-Form Health Survey, SF-36 = 36-item Short-Form Health Survey, WLQ = Work Limitations Questionnaire.

mental-interpersonal and time management tasks, as well as overall job performance, compared to nondepressed employees.[25–28] In 1 study conducted in a large company, the lost productive time associated with MDD was reported to be nearly 6 hours per week, at a cost of $44 billion annually.[28] In addition, less severe forms of depression (ie, subthreshold depressive symptoms,[29,30] minor depression,[31–33] and dysthymia[34]) also have been shown to negatively impact work functioning.

In 1 large-scale work performance study, NCS participants currently experiencing a depressive episode were compared to those with episodes that resolved >1 to 6 months ago, >6 to 12 months ago, and >12 months ago. These patients had responded to treatment but continued to experience significant residual symptoms that were more pronounced than the level seen in the euthymic controls. Patients who were currently experiencing a depressive episode were significantly more likely to experience lost days than healthy controls and those with residual symptoms; however, compared to healthy controls, depressed patients and even those with residual symptoms were significantly more likely to experience difficult days and cutback days (in which the depressed patient did not get as much done as usual) than healthy controls.[29,30]

A growing body of data has demonstrated that depressive symptoms include impairments in cognitive functioning that can result in declining work performance. A recently published study that assessed untreated MDD patients using work performance measures following an error or receipt of negative feedback demonstrates that dysfunctional information processing associated with depression can lead to declines in productivity.[19] This study and a number of other neuroimaging studies have suggested that these maladaptive cognitive processes involve areas of the brain that are thought to be associated with the symptoms of MDD (eg, the prefrontal cortex, anterior cingulate cortex, hippocampus).[19–22]

Psychosocial Functioning

The components of psychosocial functioning vary between scales and sometimes overlap with assessments of work performance but are mainly differentiated by the assessment of other areas of functioning beyond the workplace. Several studies have been conducted that support the claim that MDD has a negative impact on overall social functioning.[35,36] Results from an analysis of patients experiencing different levels of depressive symptomatology (ie, subthreshold depressive symptoms, minor depression/dysthymia, and MDD) have suggested that psychosocial disability increases correspondingly with the severity of depressive symptoms.[37] In a more recently conducted study, which assessed patients with MDD and bipolar I and II disorder, those experiencing

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

MDD were found to experience significant psychosocial impairment during the majority of follow-up visits.[38]

Quality of Life

Quality of life is difficult to concisely define due to its subjective nature and the overlap between assessing functional outcomes; therefore, measuring quality of life is more complex than the other outcomes described. For example, assessing the quality of a person's life without examining how the individual functions in his or her expected roles, in either family life or work performance, is difficult.

The impact of a major depressive episode on health-related quality of life in individuals with[39–48] or without[39–43] a general medical condition has been well established in the literature, and treating MDD to a full remission of symptoms can improve quality of life to a greater extent than when significant residual symptoms are present.[49,50]

TREATMENT OF THE FUNCTIONAL DISABILITY ASSOCIATED WITH MDD

A number of empirically supported treatment options have demonstrated effectiveness in alleviating the disability caused by MDD,[30,51–56] as well as in lowering health care costs,[49,57–65] improving quality of life,[50,66,67] and decreasing absenteeism in depressed patients,[49,68] particularly in those who receive early and adequate treatment.[69,70] For example, the Sequenced Treatment Alternatives to Relieve Depression trial, a large-scale assessment of an MDD treatment algorithm conducted in a real-world clinical setting, demonstrated that following sequential treatment alternatives for patients not reaching remission with first-line treatment can lead to significant improvements in functioning and quality of life.[53,71]

Despite increased usage of the multiple antidepressant medications available to patients and improvements in empirically supported treatment guidelines and algorithms, data are available that demonstrate that a disproportionately large number of patients continue to receive inadequate treatment for their depressive episodes. In a cross-sectional analysis of medical records from 2 cohorts of depressed patients (ie, 1993 to 1994 and 2003 to 2004), an increase in the use of adequate antidepressant doses was observed; however, the use of sequential antidepressant treatment options and psychotherapy remained low.[72]

An effective way of lowering the costs associated with MDD is to encourage physicians to use guideline-derived forms of treatment and utilize enhanced treatment options, such as incorporating care managers for monitoring the patient's symptoms, adverse events, and adherence.[73] In addition, 1 study demonstrated that by taking steps to improve employee access to effective depression treatment—for example, by lowering copayments and using a selective contracting network and a mental health destigmatization program—the likelihood of initiating treatment and having more mental health visits increased.[74]

The relationship between MDD, functional disability, and impaired quality of life has been suggested to be bidirectional. In addition to MDD negatively impacting functioning and quality of life, the presence of these impairments at baseline has been linked to poor antidepressant treatment response.[53,75,76] It also has been suggested that functional impairment and a lower quality of life are associated with an elevated risk for the recurrence of a major depressive episode.[77–79]

ASSESSING DECLINES IN FUNCTIONING AND QUALITY OF LIFE ASSOCIATED WITH MDD

Table 2 describes some commonly used functional outcome measures and assessments of quality of life. The 36-item Short-Form Health Survey (SF-36)[80] was the most widely used scale in the studies identified during our systematic review of the literature. Its length and complexity have been impediments to its regular use in clinical settings; however, a shortened 12-item version (SF-12) is also available that may be better suited for use in busy practice settings.[81] In addition, the Sheehan Disability Scale (SDS)[82] and the Work Limitations Questionnaire (WLQ)[83] were commonly used. The SDS is widely used in research settings because it has been shown to be sensitive to treatment effects, and its concise means of assessing the overall level of functioning make it desirable for use in clinical settings as well.

The World Health Organization 5-item Well-Being Index,[84] Social Adjustment Scale–Self-Report (SAS-SR),[85] and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[86] are commonly used to assess psychosocial functioning and quality of life, whereas the Endicott Work Productivity Scale,[87] Work Productivity and Activity Impairment Questionnaire,[88] and WLQ[83] are commonly used assessments of work dysfunction.

Perhaps the most familiar means of assessing the functional declines associated with psychiatric disorders is Axis V of the multiaxial diagnostic methodology used in the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*.[89] The Global Assessment of Functioning (GAF) asks the clinician to rate the level of functioning in relation to symptom severity. This combination of 2 distinct outcomes on 1 axis has been the primary criticism of the GAF, as a separation between these outcomes is important to obtaining an accurate level of functional disability independent of symptom severity. In addition, the Global Assessment of Relational Functioning (GARF) and Social and Occupational Functioning Assessment Scale (SOFAS) were designed as supplemental assessments

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

Table 2. Commonly Used Assessments of Functioning and Quality of Life

Scale	Number of Items	Areas of Assessment	Rating Scale
36-Item Short-Form Health Survey[80]	36 patient-rated items	8 subscales: physical functioning, role-physical, bodily pain, general health perception, vitality, social functioning, role-emotional, mental health	Items are rated numerically either with a Likert scale (1 to 5 and 1 to 6) or with yes (1) or no (2) responses
Endicott Work Productivity Scale[87]	25 patient-rated items	Assesses how medical disorders impact work performance across a range of activities (eg, pace of work, organization, prioritizing, not performing expected tasks)	Items are generally rated on a 5-point scale (0 [never] to 4 [almost always]); there are also open-ended items that ask patients the number of hours worked and to provide a reason why fewer hours than expected have been worked
Global Assessment of Functioning (GAF), Social and Occupational Functioning Assessment Scale (SOFAS), Global Assessment of Relational Functioning (GARF)[89]	Each scale provides 1 score that assesses functioning	GAF: Measures social, occupational, and psychological functioning in relation to psychiatric symptom severity	GAF: 10 categorical ratings each within a 10-point range (ie, 100 to 91: superior functioning; 10 to 1: nonfunctioning [ie, violent, suicidal, persistent lack of hygiene])
		SOFAS: Measures social and occupational functioning independent of symptom severity	SOFAS: 10 categorical ratings each within a 10-point range (ie, 100 to 91: superior functioning; 90 to 81: good functioning with minimal, socially appropriate symptomatology; 80 to 71: transient and minimal impairment)
		GARF: 3 major content areas associated with familial and other social relationships: problem solving, organization, emotional climate	GARF: 5 categories with scores ranging from 100 to 81 (relational unit is functioning satisfactorily) to 20 to 1 (relational unit has become too dysfunctional to retain continuity of contact and attachment)
Quality of Life Enjoyment and Satisfaction Questionnaire[86]	93 items	5 subscales: physical health, subjective feelings, leisure time activities, social relationships, general activities 3 scales that are appropriate for each patient: work, household duties, school/course work	Items are rated on a 5-point scale (0 [never] to 4 [almost always]) and generally follow the same format: During the past week, how often have you been pleased with your work accomplishments, kept your room/apartment/house cleaned to your satisfaction, shopped for food or other household items to your satisfaction, and joked or laughed with other people?
Sheehan Disability Scale[82]	3 patient-rated items	Work/school, social life, family life functioning	Combination of visual, verbal, and numerical anchors (0 [not at all] to 10 [extremely]) ≥ 5 on any item is indicative of impaired functioning
Social Adjustment Scale–Self-Report[85]	42 items divided into 4 categories: performance, friction, finer aspects of relationships, inner feelings/satisfaction	Work, social/leisure, extended family, and marital, parental, and familial relationships	5-point Likert scale with higher scores indicating a greater level of impairment; total score can be obtained by adding the individual item scores then dividing by the number of items that have actually been scored
Work Limitations Questionnaire[83]	25 items	4 subscales: time demands (5 items), physical demands (6 items), mental-interpersonal demands (9 items), output demands (5 items)	Scores range from 0 (limited none of the time) to 100 (limited all of the time) and represent the reported amount of time in the prior 2 wk respondents experienced work limitations; additionally, using an algorithm, Work Limitations Questionnaire scores can be converted into an estimate of productivity loss
Work Productivity and Activity Impairment Questionnaire[88]	6 items	Assesses patients on the number of hours lost during the last days due to the patient's "problem" or any other reason, the number of hours worked, and the effect the patient's "problem" has on productivity at work and on other activities	An overall work productivity score and a quantification of overall work productivity and impairment in regular activities are obtained
World Health Organization 5-Item Well-Being Index[84]	5 patient-rated, depression-specific items	Cheerful/good spirits, calm/relaxed, active/vigorous, wake feeling fresh/rested, life is full of things that interest me	Rated on a 0 (at no time) to 5 (all of the time) Likert scale A score of 25 represents the best possible quality of life, and a score < 13 is indicative of a diagnosis of major depressive disorder

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

of functioning to be used in conjunction with the GAF.[89] The GARF was specifically designed to assess familial and other long-term relationships, whereas the SOFAS was designed to assess social and occupational functioning independent of symptom severity.[89]

ISSUES ASSOCIATED WITH USING "REAL-WORLD" OUTCOME MEASURES

Despite the benefits of assessing functioning and quality of life to the various stakeholders involved with the treatment of MDD, the potential issues associated with using such scales must be noted. Some of the commonly used assessment tools described above have some unmet needs. Namely, they can be cumbersome for use in the clinical setting because they are generally too lengthy to administer in the ever-lessening duration of clinical visits. As was previously mentioned, a number of these scales, such as the SF-36, WLQ, SAS-SR, and Q-LES-Q, are thought to be too lengthy for use during clinical visits. In addition, there is some ambiguity as to what these scales actually measure, mainly due to the lack of consistency in the items they use and the lack of a clear gold standard. On the other hand, some scales are too specific. The assessments of work functioning, for example, focus too narrowly on the area of work dysfunction to be used alone in a clinical setting wherein a level of overall functional status is desired.

When performing follow-up assessments using these scales, it is important to note that a lag time in improvements in functional impairment has been observed in relation to improvements in depressive symptomatology. When assessing functioning, > 8 weeks may be required before improvements are observed, whereas improvements in depressive symptoms generally occur sooner.[90,91] A secondary analysis of data from a randomized trial investigating selective serotonin reuptake inhibitor treatment,[92] which calls for a broader definition of depression remission that expands beyond symptom severity, demonstrated that depressive symptoms improve in synchrony and are correlated with work functioning, even though depressive symptoms improved to a greater degree. It is also important to note that the majority of the scales described above are not designed to diagnose MDD and are meant only to be used for screening and to assess and monitor changes in disability. If the results are suggestive of a depressive disorder, then a validated diagnostic assessment tool should be used to make a proper diagnosis.

CONCLUSIONS

The development of an assessment tool that can address the issues described above would be a benefit to the various parties involved with the treatment of MDD (eg, researchers, patients, health care plans). The SDS has many positive attributes but has not yet been widely accepted as the gold standard in assessing disability in patients with MDD. The limitations of the SDS include its assessment of patients on only 3 domains of functioning and the lack of a depression-specific focus. The SF-12, a shortened version of the SF-36, is another valuable assessment tool due to its more detailed assessment of disability yet compact enough length for use in clinical practice. Perhaps creating a "hybrid" scale adopting the best of various options that can become a standard measure for assessing the disability associated with MDD will become necessary. Along with assessing the impact on the emotional and physical symptoms of MDD, assessing functional disability and declines in quality of life should continue to become a routine part of clinical care and outcome measures in clinical trials that assess the efficacy of antidepressant treatment.[43,78,93,94] As calls for the measurement-based care of MDD continue, particularly for primary care physicians, a thorough assessment of the impact that MDD has on a patient's life will become a necessity.

Author affiliations: The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Dr Langlieb) and Pfizer Inc, formerly Wyeth Research, Collegeville, Pennsylvania (Dr Guico-Pabia).
Author contributions: Drs Langlieb and Guico-Pabia equally contributed to the study by analyzing and interpreting data, drafting and revising the manuscript, and obtaining funding.
Potential conflicts of interest: **Dr Langlieb** serves on the advisory boards for Eli Lilly and Pfizer Inc. **Dr Guico-Pabia** is an employee of Pfizer Inc, formerly Wyeth Research.
Funding/support: This analysis was supported by Wyeth Research, Collegeville, Pennsylvania, which was acquired by Pfizer Inc in October 2009.
Acknowledgment: Medical writing/editing support was funded by Wyeth Research. Dennis A. Stancavish, MA, provided writing support and editing support was provided by Jennifer B. Karpinski, BA, both of Embryon, LLC, A Division of Advanced Health Media, LLC (formerly Medesta Publications Group, A Business of Advogent).

REFERENCES

1. Kessler RC, Berglund P, Demler O, et al. National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095–3105.
2. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*. 1997;349(9063):1436–1442.
3. World Health Organization. *The World Health Report: 2001–Mental Health: New Understanding, New Hope*. Geneva, Switzerland: World Health Organization; 2001.
4. Thrall G, Lane D, Carroll D, et al. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med*. 2006;119(5):448–519, e1–e19.
5. Williams RG, Pearson GD, Barst RJ, et al. Report of the National Heart, Lung, and Blood Institute Working Group on research in adult congenital heart disease. *J Am Coll Cardiol*. 2006;47(4):701–707.
6. Huang IC, Hwang CC, Wu MY, et al. Diabetes-specific or generic measures for health-related quality of life? evidence from psychometric validation of the D-39 and SF-36. *Value Health*. 2008;11(3):450–461.
7. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? *J Clin Psychiatry*. 2003;64(12):1465–1475.

© Copyright 2010 Physicians Postgraduate Press, Inc © Copyright 2010 Physicians Postgraduate Press, Inc

8. Birnbaum HG, Leong SA, Greenberg PE. The economics of women and depression: an employer's perspective. *J Affect Disord*. 2003;74(1):15–22.
9. Kessler RC, Akiskal HS, Ames M, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of US workers. *Am J Psychiatry*. 2006;163(9):1561–1568.
10. Druss BG, Rosenheck RA, Sledge WH. Health and disability costs of depressive illness in a major US corporation. *Am J Psychiatry*. 2000;157(8):1274–1278.
11. Gameroff MJ, Olfson M. Major depressive disorder, somatic pain, and health care costs in an urban primary care practice. *J Clin Psychiatry*. 2006;67(8):1232–1239.
12. Emptage NP, Sturm R, Robinson RL. Depression and comorbid pain as predictors of disability, employment, insurance status, and health care costs. *Psychiatr Serv*. 2005;56(4):468–474.
13. Katon WJ, Lin E, Russo J, et al. Increased medical costs of a population-based sample of depressed elderly patients. *Arch Gen Psychiatry*. 2003;60(9):897–903.
14. Simon GE, Katon WJ, Lin EH, et al. Diabetes complications and depression as predictors of health service costs. *Gen Hosp Psychiatry*. 2005;27(5):344–351.
15. Katon WJ, Rutter C, Simon G, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care*. 2005;28(11):2668–2672.
16. Barefoot JC, Helms MJ, Mark DB, et al. Depression and long-term mortality risk in patients with coronary artery disease. *Am J Cardiol*. 1996;78(6):613–617.
17. Kaufmann MW, Fitzgibbons JP, Sussman EJ, et al. Relation between myocardial infarction, depression, hostility, and death. *Am Heart J*. 1999;138(3, pt 1):549–554.
18. Wittchen HU, Carter RM, Pfister H, et al. Disabilities and quality of life in pure and comorbid generalized anxiety disorder and major depression in a national survey. *Int Clin Psychopharmacol*. 2000;15(6):319–328.
19. Holmes AJ, Pizzagalli DA. Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Arch Gen Psychiatry*. 2008;65(2):179–188.
20. Mondal S, Sharma VK, Das S, et al. Neuro-cognitive functions in patients of major depression. *Indian J Physiol Pharmacol*. 2007;51(1):69–75.
21. Smith DJ, Muir WJ, Blackwood DH. Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder and recurrent major depressive disorder. *Bipolar Disord*. 2006;8(1):40–46.
22. Wang PS, Beck AL, Berglund P, et al. Effects of major depression on moment-in-time work performance. *Am J Psychiatry*. 2004;161(10):1885–1891.
23. Lerner D, Adler DA, Chang H, et al. Unemployment, job retention, and productivity loss among employees with depression. *Psychiatr Serv*. 2004;55(12):1371–1378.
24. Marcotte DE, Wilcox-Gök V, Redmon PD. Prevalence and patterns of major depressive disorder in the United States labor force. *J Ment Health Policy Econ*. 1999;2(3):123–131.
25. Adler DA, McLaughlin TJ, Rogers WH, et al. Job performance deficits due to depression. *Am J Psychiatry*. 2006;163(9):1569–1576.
26. Berndt ER, Finkelstein SN, Greenberg PE, et al. Workplace performance effects from chronic depression and its treatment. *J Health Econ*. 1998;17(5):511–535.
27. Druss BG, Schlesinger M, Allen HM Jr. Depressive symptoms, satisfaction with health care, and 2-year work outcomes in an employed population. *Am J Psychiatry*. 2001;158(5):731–734.
28. Stewart WF, Ricci JA, Chee E, et al. Cost of lost productive work time among US workers with depression. *JAMA*. 2003;289(23):3135–3144.
29. Mojtabai R. Residual symptoms and impairment in major depression in the community. *Am J Psychiatry*. 2001;158(10):1645–1651.
30. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. *JAMA*. 1989;262(7):914–919.
31. Backenstrass M, Frank A, Joest K, et al. A comparative study of nonspecific depressive symptoms and minor depression regarding functional impairment and associated characteristics in primary care. *Compr Psychiatry*. 2006;47(1):35–41.
32. Cuijpers P, de Graaf R, van Dorsselaer S. Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. *J Affect Disord*. 2004;79(1–3):71–79.
33. Wagner HR, Burns BJ, Broadhead WE, et al. Minor depression in family practice: functional morbidity, co-morbidity, service utilization and outcomes. *Psychol Med*. 2000;30(6):1377–1390.
34. Adler DA, Irish J, McLaughlin TJ, et al. The work impact of dysthymia in a primary care population. *Gen Hosp Psychiatry*. 2004;26(4):269–276.
35. Spitzer RL, Kroenke K, Linzer M, et al. Health-related quality of life in primary care patients with mental disorders: results from the PRIME-MD 1000 Study. *JAMA*. 1995;274(19):1511–1517.
36. Saarijärvi S, Salminen JK, Toikka T, et al. Health-related quality of life among patients with major depression. *Nord J Psychiatry*. 2002;56(4):261–264.
37. Judd LL, Akiskal HS, Zeller PJ, et al. Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch Gen Psychiatry*. 2000;57(4):375–380.
38. Judd LL, Schettler PJ, Solomon DA, et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. *J Affect Disord*. 2008;108(1-2):49–58.
39. Cronin-Stubbs D, de Leon CF, Beckett LA, et al. Six-year effect of depressive symptoms on the course of physical disability in community-living older adults. *Arch Intern Med*. 2000;160(20):3074–3080.
40. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry*. 2007;29(2):147–155.
41. Stein MB, Cox BJ, Afifi TO, et al. Does co-morbid depressive illness magnify the impact of chronic physical illness? a population-based perspective. *Psychol Med*. 2006;36(5):587–596.
42. Strine TW, Chapman DP, Kobau R, et al. Depression, anxiety, and physical impairments and quality of life in the US noninstitutionalized population. *Psychiatr Serv*. 2004;55(12):1408–1413.
43. Trivedi MH, Rush AJ, Wisniewski SR, et al. Factors associated with health-related quality of life among outpatients with major depressive disorder: a STAR*D report. *J Clin Psychiatry*. 2006;67(2):185–195.
44. Baune BT, Adrian I, Jacobi F. Medical disorders affect health outcome and general functioning depending on comorbid major depression in the general population. *J Psychosom Res*. 2007;62(2):109–118.
45. Beekman AT, Penninx BW, Deeg DJ, et al. The impact of depression on the well-being, disability and use of services in older adults: a longitudinal perspective. *Acta Psychiatr Scand*. 2002;105(1):20–27.
46. Dorenlot P, Harboun M, Bige V, et al. Major depression as a risk factor for early institutionalization of dementia patients living in the community. *Int J Geriatr Psychiatry*. 2005;20(5):471–478.
47. Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *Gen Hosp Psychiatry*. 2007;29(5):409–416.
48. Papapetropoulos S, Ellul J, Argyriou AA, et al. The effect of depression on motor function and disease severity of Parkinson's disease. *Clin Neurol Neurosurg*. 2006;108(5):465–469.
49. Simon GE, Revicki D, Heiligenstein J, et al. Recovery from depression, work productivity, and health care costs among primary care patients. *Gen Hosp Psychiatry*. 2000;22(3):153–162.
50. Angermeyer MC, Holzinger A, Matschinger H, et al. Depression and quality of life: results of a follow-up study. *Int J Soc Psychiatry*. 2002;48(3):189–199.
51. Dombrovski AY, Lenze EJ, Dew MA, et al. Maintenance treatment for old-age depression preserves health-related quality of life: a randomized, controlled trial of paroxetine and interpersonal psychotherapy. *J Am Geriatr Soc*. 2007;55(9):1325–1332.
52. Keller MB, Trivedi MH, Thase ME, et al. The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study: outcomes from the 2-year and combined maintenance phases. *J Clin Psychiatry*. 2007;68(8):1246–1256.
53. Trivedi MH, Rush AJ, Wisniewski SR, et al. STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28–40.
54. Wang PS, Patrick A, Avorn J, et al. The costs and benefits of enhanced depression care to employers. *Arch Gen Psychiatry*. 2006;63(12):1345–1353.
55. Wang PS, Simon GE, Avorn J, et al. Telephone screening, outreach, and care management for depressed workers and impact on clinical and work productivity outcomes: a randomized controlled trial. *JAMA*. 2007;298(12):1401–1411.

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

56. Zhang M, Rost KM, Fortney JC. Earnings changes for depressed individuals treated by mental health specialists. *Am J Psychiatry*. 1999;156(1):108–114.
57. Goldman W, McCulloch J, Cuffel B, et al. Outpatient utilization patterns of integrated and split psychotherapy and pharmacotherapy for depression. *Psychiatr Serv*. 1998;49(4):477–482.
58. Hankin JR, Kessler LG, Goldberg ID, et al. A longitudinal study of offset in the use of nonpsychiatric services following specialized mental health care. *Med Care*. 1983;21(11):1099–1110.
59. Leon AC, Walkup JT, Portera L. Assessment and treatment of depression in disability claimants: a cost-benefit simulation study. *J Nerv Ment Dis*. 2002;190(1):3–9.
60. Von Korff M, Katon W, Bush T, et al. Treatment costs, cost offset, and cost-effectiveness of collaborative management of depression. *Psychosom Med*. 1998;60(2):143–149.
61. Von Korff M, Katon W, Rutter C, et al. Effect on disability outcomes of a depression relapse prevention program. *Psychosom Med*. 2003;65(6):938–943.
62. Araya R, Flynn T, Rojas G, et al. Cost-effectiveness of a primary care treatment program for depression in low-income women in Santiago, Chile. *Am J Psychiatry*. 2006;163(8):1379–1387.
63. Aziz M, Mehringer AM, Mozurkewich E, et al. Cost-utility of 2 maintenance treatments for older adults with depression who responded to a course of electroconvulsive therapy: results from a decision analytic model. *Can J Psychiatry*. 2005;50(7):389–397.
64. Mitchell J, Greenberg J, Finch K, et al. Effectiveness and economic impact of antidepressant medications: a review. *Am J Manag Care*. 1997;3(2):323–330, quiz 331.
65. von Knorring L, Akerblad AC, Bengtsson F, et al. Cost of depression: effect of adherence and treatment response. *Eur Psychiatry*. 2006;21(6):349–354.
66. Berlim MT, Pargendler J, Brenner J, et al. Significant improvement in the quality of life of Brazilian depressed outpatients 12 weeks following the start of antidepressants. *Psychiatry Res*. 2007;153(3):253–259.
67. Vos T, Haby MM, Barendregt JJ, et al. The burden of major depression avoidable by longer-term treatment strategies. *Arch Gen Psychiatry*. 2004;61(11):1097–1103.
68. Claxton AJ, Chawla AJ, Kennedy S. Absenteeism among employees treated for depression. *J Occup Environ Med*. 1999;41(7):605–611.
69. Dewa CS, Hoch JS, Lin E, et al. Pattern of antidepressant use and duration of depression-related absence from work. *Br J Psychiatry*. 2003;183(6):507–513.
70. Rizzo JA, Abbott TA 3rd, Pashko S. Labour productivity effects of prescribed medicines for chronically ill workers. *Health Econ*. 1996;5(3):249–265.
71. Trivedi MH, Fava M, Wisniewski SR, et al. STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1243–1252.
72. Honkonen TI, Aro TA, Isometsä ET, et al. Quality of treatment and disability compensation in depression: comparison of 2 nationally representative samples with a 10-year interval in Finland. *J Clin Psychiatry*. 2007;68(12):1886–1893.
73. Lo Sasso AT, Rost K, Beck A. Modeling the impact of enhanced depression treatment on workplace functioning and costs: a cost-benefit approach. *Med Care*. 2006;44(4):352–358.
74. Lo Sasso AT, Lindrooth RC, Lurie IZ, et al. Expanded mental health benefits and outpatient depression treatment intensity. *Med Care*. 2006;44(4):366–372.
75. Bagby RM, Ryder AG, Cristi C. Psychosocial and clinical predictors of response to pharmacotherapy for depression. *J Psychiatry Neurosci*. 2002;27(4):250–257.
76. Lenze EJ, Miller MD, Dew MA, et al. Subjective health measures and acute treatment outcomes in geriatric depression. *Int J Geriatr Psychiatry*. 2001;16(12):1149–1155.
77. Solomon DA, Leon AC, Endicott J, et al. Psychosocial impairment and recurrence of major depression. *Compr Psychiatry*. 2004;45(6):423–430.
78. Solomon DA, Leon AC, Coryell W, et al. Predicting recovery from episodes of major depression. *J Affect Disord*. 2008;107(1–3):285–291.
79. Sotsky SM, Glass DR, Shea MT, et al. Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. *Am J Psychiatry*. 1991;148(8):997–1008.
80. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51(11):1055–1068.
81. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36), I: conceptual framework and item selection. *Med Care*. 1992;30(6):473–483.
82. Sheehan DV. Sheehan Disability Scale. In: Rush AJ, Pincus HA, First MB, et al, eds. *Handbook of Psychiatric Measures*. 1st ed. Washington, DC: American Psychiatric Association; 2000:113–115.
83. Lerner D, Amick BC 3rd, Rogers WH, et al. The Work Limitations Questionnaire. *Med Care*. 2001;39(1):72–85.
84. World Health Organization. *Wellbeing Measures in Primary Health Care/the Depcare Project*. Copenhagen, Denmark: WHO Regional Office for Europe; 1998.
85. Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. *Arch Gen Psychiatry*. 1976;33(9):1111–1115.
86. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull*. 1993;29(2):321–326.
87. Endicott J, Nee J. Endicott Work Productivity Scale (EWPS): a new measure to assess treatment effects. *Psychopharmacol Bull*. 1997;33(1):13–16.
88. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353–365.
89. American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
90. Bech P, Lunde M, Undén M. Social Adaptation Self-evaluation Scale (SASS): psychometric analysis as outcome measure in the treatment of patients with major depression in the remission phase. *Int J Psychiatry Clin Pract*. 2002;6:141–146.
91. Hirschfeld RM, Dunner DL, Keitner G, et al. Does psychosocial functioning improve independent of depressive symptoms? a comparison of nefazodone, psychotherapy, and their combination. *Biol Psychiatry*. 2002;51(2):123–133.
92. Aikens JE, Kroenke K, Nease DE Jr, et al. Trajectories of improvement for six depression-related outcomes. *Gen Hosp Psychiatry*. 2008;30(1):26–31.
93. Bech P. Social functioning: should it become an endpoint in trials of antidepressants? *CNS Drugs*. 2005;19(4):313–324.
94. Weissman MM. Social functioning and the treatment of depression. *J Clin Psychiatry*. 2000;61(suppl 1):33–38.
95. Arnow BA, Hunkeler EM, Blasey CM, et al. Comorbid depression, chronic pain, and disability in primary care. *Psychosom Med*. 2006;68(2):262–268.
96. Breslau N, Lipton RB, Stewart WF, et al. Comorbidity of migraine and depression: investigating potential etiology and prognosis. *Neurology*. 2003;60(8):1308–1312.
97. Breslin FC, Gnam W, Franche RL, et al. Depression and activity limitations: examining gender differences in the general population. *Soc Psychiatry Psychiatr Epidemiol*. 2006;41(8):648–655.
98. Burton WN, Pransky G, Conti DJ, et al. The association of medical conditions and presenteeism. *J Occup Environ Med*. 2004;46(suppl 6):S38–S45.
99. Carta MG, Hardoy MC, Kovess V, et al. Could health care costs for depression be decreased if the disorder were correctly diagnosed and treated? *Soc Psychiatry Psychiatr Epidemiol*. 2003;38(9):490–492.
100. Cramer JA, Blum D, Reed M, et al. Epilepsy Impact Project Group. The influence of comorbid depression on seizure severity. *Epilepsia*. 2003;44(12):1578–1584.
101. Druss BG, Rosenheck RA. Patterns of health care costs associated with depression and substance abuse in a national sample. *Psychiatr Serv*. 1999;50(2):214–218.
102. Egede LE. Diabetes, major depression, and functional disability among US adults. *Diabetes Care*. 2004;27(2):421–428.
103. Ford JD, Trestman RL, Steinberg K, et al. Prospective association of anxiety, depressive, and addictive disorders with high utilization of primary, specialty and emergency medical care. *Soc Sci Med*. 2004;58(11):2145–2148.
104. Frasure-Smith N, Lespérance F, Talajic M. Depression following myocardial infarction: impact on 6-month

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.

survival. *JAMA*. 1993;270(15):1819–1825.
105. Haarasilta L, Marttunen M, Kaprio J, et al. Major depressive episode and physical health in adolescents and young adults: results from a population-based interview survey. *Eur J Public Health*. 2005;15(5):489–493.
106. Hoge CW, Lesikar SE, Guevara R, et al. Mental disorders among US military personnel in the 1990s: association with high levels of health care utilization and early military attrition. *Am J Psychiatry*. 2002;159(9):1576–1583.
107. Janssens AC, van Doorn PA, de Boer JB, et al. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. *Mult Scler*. 2003;9(4):397–403.
108. Keenan-Miller D, Hammen CL, Brennan PA. Health outcomes related to early adolescent depression. *J Adolesc Health*. 2007;41(3):256–262.
109. Kessler RC, Barber C, Birnbaum HG, et al. Depression in the workplace: effects on short-term disability. *Health Aff (Millwood)*. 1999;18(5):163–171.
110. Kessler RC, Ormel J, Demler O, et al. Comorbid mental disorders account for the role impairment of commonly occurring chronic physical disorders: results from the National Comorbidity Survey. *J Occup Environ Med*. 2003;45(12):1257–1266.
111. Kouzis AC, Eaton WW. Emotional disability days: prevalence and predictors. *Am J Public Health*. 1994;84(8):1304–1307.
112. Lerner D, Adler DA, Chang H, et al. The clinical and occupational correlates of work productivity loss among employed patients with depression. *J Occup Environ Med*. 2004;46(suppl 6):S46–S55.
113. Lespérance F, Frasure-Smith N, Talajic M, et al. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation*. 2002;105(9):1049–1053.
114. Luber MP, Hollenberg JP, Williams-Russo P, et al. Diagnosis, treatment, comorbidity, and resource utilization of depressed patients in a general medical practice. *Int J Psychiatry Med*. 2000;30(1):1–13.
115. McIntyre RS, Wilkins K, Gilmour H, et al. The effect of bipolar I disorder and major depressive disorder on workforce function. *Chronic Dis Can*. 2008;28(3):84–91.
116. McQuaid JR, Stein MB, Laffaye C, et al. Depression in a primary care clinic: the prevalence and impact of an unrecognized disorder. *J Affect Disord*. 1999;55(1):1–10.
117. Muchmore L, Lynch WD, Gardner HH, et al. Prevalence of arthritis and associated joint disorders in an employed population and the associated healthcare, sick leave, disability, and workers' compensation benefits cost and productivity loss of employers. *J Occup Environ Med*. 2003;45(4):369–378.
118. Martínez-Martín P, Gil-Nagel A, Gracia LM, et al; The Cooperative Multicentric Group. Unified Parkinson's Disease Rating Scale characteristics and structure. *Mov Disord*. 1994;9(1):76–83.
119. Ginanneschi A, Degl'Innocenti F, Magnolfi S, et al. Evaluation of Parkinson's disease: reliability of three rating scales. *Neuroepidemiology*. 1988;7(1):38–41.
120. Schwab RS, England AC Jr. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson MC, eds. *Third Symposium of Parkinson's Disease*. Edinburgh, Scotland: E&S Livingstone; 1969:152–157.
121. Penninx BW, Beekman AT, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry*. 2001;58(3):221–227.
122. Rovner BW. Depression and increased risk of mortality in the nursing home patient. *Am J Med*. 1993;94(5A):19S–22S.
123. Rumsfeld JS, Magid DJ, Plomondon ME, et al. History of depression, angina, and quality of life after acute coronary syndromes. *Am Heart J*. 2003;145(3):493–499.
124. Simon GE, VonKorff M, Barlow W. Health care costs of primary care patients with recognized depression. *Arch Gen Psychiatry*. 1995;52(10):850–856.
125. Sobocki P, Jönsson B, Angst J, et al. Cost of depression in Europe. *J Ment Health Policy Econ*. 2006;9(2):87–98.
126. Sullivan MD, LaCroix AZ, Baum C, et al. Functional status in coronary artery disease: a one-year prospective study of the role of anxiety and depression. *Am J Med*. 1997;103(5):348–356.
127. Sullivan MD, LaCroix AZ, Spertus JA, et al. Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. *Am J Cardiol*. 2000;86:1135–1138, A6, A9.
128. Unützer J, Patrick DL, Simon G, et al. Depressive symptoms and the cost of health services in HMO patients aged 65 years and older: a 4-year prospective study. *JAMA*. 1997;277(20):1618–1623.

© Copyright 2010 Physicians Postgraduate Press, Inc. © Copyright 2010 Physicians Postgraduate Press, Inc.