

Effect of Inadequate Response to Treatment in Patients With Depression

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Objectives: To assess the effects of inadequate response to antidepressant treatment on healthcare resource utilization and on work productivity in patients diagnosed as having major depressive disorder (MDD).

Study Design: This study used data from the 2006 US National Health and Wellness Survey, a cross-sectional survey of adults 18 years and older.

Methods: Patients who self-reported a confirmed diagnosis of depression and were currently taking antidepressant medication were included in the analyses. Adequacy of antidepressant treatment response was determined from responses to the mental health domain of the 8-Item Short Form Health Survey (SF-8). Logistic regression analyses adjusted for demographics, comorbidity, and component scores on the SF-8 were used to determine the associations between inadequacy of treatment response and health outcomes.

Results: Of 5988 patients who met the inclusion criteria for the study, 30.9% were classified as antidepressant treatment responders, 31.2% were partial responders, and 37.9% were non-responders. Partial response and nonresponse to treatment were associated with greater likelihood of emergency department utilization (odds ratios [ORs], 1.26 and 1.54, respectively; $P < .01$ for both) and hospitalization (OR, 1.23; $P = .05$ and OR, 1.39; $P < .01$, respectively). Similarly, partial response and nonresponse were associated with lower likelihood of current employment (OR, 0.83; $P = .01$ and OR, 0.63; $P < .01$, respectively) and with greater likelihood of work productivity loss among the employed (ORs, 1.42 and 1.99, respectively; $P < .01$ for both).

Conclusions: Patients with MDD who failed to respond to antidepressant treatment as evidenced by poor self-reported mental health status used more healthcare resources, were less likely to be employed, and had more work productivity loss than those who responded to antidepressant therapy.

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For author information and disclosures,
see end of text.

Major depressive disorder (MDD) is a serious mental illness characterized by 1 or more major depressive episodes.¹ There are several therapies available to treat MDD.² Initial first-line therapies include the following 3 classes of medications: selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and a norepinephrine-dopamine reuptake inhibitor. Older medications such as tricyclic antidepressants and monoamine oxidase inhibitors are typically used only if the patient has not responded to the first-line therapies.³ *Treatment response* is usually defined as (1) at least 50% improvement on a depression rating scale, typically the Hamilton Rating Scale for Depression, or (2) “much improved” or “very much improved” on the Clinical Global Impressions–Severity of Illness and Clinical Global Impressions–Improvement scales.⁴ The ultimate goal of therapy is remission, whereby there is an absence of depressive symptoms.³ Between response and nonresponse lies *partial response*, which is often defined as (1) less than 50% but at least 25% improvement on a depression scale, or (2) “minimal improvement” on the Clinical Global Impressions–Improvement scale.^{4,5}

Unfortunately, the treatment of MDD continues to pose a challenge, and 50% to 70% of patients do not fulfill conventional remission criteria following treatment with at least 1 antidepressant of adequate dosage and duration in clinical trials.^{4,6–8} Determining treatment resistance prevalence is difficult because definitions vary, but most researchers agree that a patient is considered to have treatment-resistant or treatment-refractory depression (TRD) when at least 2 trials of antidepressants from different pharmacologic classes fail to result in remission.⁹ Management of TRD involves evaluating the patient for possible conditions that may affect treatment response and using 1 of the following 4 pharmacologic options for increasing efficacy: optimizing, augmenting, combining, and switching.⁹ The Sequenced Treatment Alternatives to Relieve Depression study,¹⁰ a large-scale clinical trial, found that no second-generation antidepressant was more effective than another as a second-line treatment.

In 2000, the total economic burden of treating depression in the United States was \$83.1 billion, with workplace costs (including missed workdays and lack of productivity because of illness) accounting for 62% of the total economic burden; other economic burdens included \$26.1 billion (31% of

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the total) for treatment costs and \$5.4 billion (7%) for suicide-related costs.¹¹ Using medical claims data from 1995 to 2000, Crown et al¹² estimated that patients with TRD were at least twice as likely to be hospitalized (for general medical and depression-related conditions) and had at least 12% more outpatient visits compared with patients with depression that did not meet the TRD criteria.

Studies examining depression and lost productivity have typically examined direct costs or indirect costs, and most have not examined costs by treatment response or addressed costs related to presenteeism (impairment while working), absenteeism (missed work), or overall work productivity loss (combination of absenteeism and presenteeism). Our goal was to focus on patients diagnosed as having MDD and currently being treated to determine the consequences of inadequate response to antidepressant treatment. Specifically, the objective was to provide a more complete cost picture using patient-reported outcomes to assess the effects of inadequate response to antidepressant treatment on healthcare resource utilization, work productivity, and activity loss in a large nationwide sample of patients diagnosed as having MDD.

METHODS

Study Design

This was a cross-sectional study. Data were taken from the 2006 US National Health and Wellness Survey (NHWS), an annual cross-sectional study of approximately 63,000 adults 18 years and older. Potential participants were contacted by the Lightspeed Research (LSR) (Basking Ridge, NJ) Internet panel. Members of the panel were recruited through opt-in e-mail, coregistration with LSR partners, e-newsletter campaigns, banner placements, and internal and external affiliate networks. All potential panelists had to register with the panel through a unique e-mail address and password and had to complete an in-depth demographic registration profile. In total, 1,494,260 members of the LSR panel were contacted to complete the NHWS survey in 2006, and 62,833 responded (4.2% response rate). A stratified random sample procedure was implemented to ensure that the demographic distribution of the responders was equivalent to that of the total US population. Comparisons between the NHWS survey and other national databases have been highlighted elsewhere.¹³

The 2006 US NHWS consisted of information on demographics, healthcare attitudes and behaviors, disease status, and outcomes. All data were self-reported directly by patients

Take-Away Points

Patients with inadequate response to depression treatment used increased healthcare resources and had more presenteeism than those with treatment response.

- For patients diagnosed as having major depressive disorder (MDD) and treated with antidepressant medication, inadequate response to therapy was associated with healthcare resource utilization that included emergency department and inpatient services.
- Inadequate response to antidepressants was associated with lower likelihood of employment and with greater likelihood of work productivity loss among the employed.
- Because inadequate treatment had cost consequences for health plans and for employers, encouraging improvements in the adequacy of treatment for patients with MDD should be of interest to both parties.

through self-administered Internet-based questionnaires. The NHWS sampling frame consisted of quotas based on sex, age, and race/ethnicity to reflect the demographic population of the US adult population; in addition, the NHWS is geographically representative of the entire United States. The NHWS questionnaire and study protocol were approved by Essex Institutional Review Board, Inc (Lebanon, NJ). Informed consent was obtained from respondents before entering the survey.

Study Sample

The study sample consisted of participants in the 2006 US NHWS who met the following study criteria: (1) received a diagnosis of depression from a health professional (“Has your depression been diagnosed by a health professional? Yes or no.”) and (2) currently taking an antidepressant medication (“Please indicate which of the following prescription medications you currently use to treat your depression. Please select all that apply.”) Respondents who self-reported a diagnosis of depression and current use of antidepressant medication were included in the analyses. Respondents who self-reported a diagnosis of bipolar disorder or current use of antipsychotic medication were excluded from the analyses.

The study sample was then stratified based on self-reported current mental health status using the mental health domain of the 8-Item Short Form Health Survey (SF-8). The SF-8 consists of 8 questions that correspond directly to 8 subscales of the 36-Item Short Form Health Survey. These 8 subscales are physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. A mental health component summary score and a physical component summary score are derived from the SF-8. For both summary measures, the mean (SD) normative score for the US population is 50 (10), with higher scores indicating better physical or mental well-being.¹⁴

Sample stratification was based on participant response to the following question on the SF-8: “During the past 4 weeks, how much have you been bothered by emotional problems

(such as feeling anxious, depressed, or irritable?). Response options included “not at all,” “slightly,” “moderately,” “quite a lot,” or “extremely.” Respondents were stratified into 1 of the following 3 groups: *treatment responders* (defined by a response of “not at all” or “slightly” and used as the reference group in regression analyses), *partial responders* (defined by a response of “moderately”), or *nonresponders* (defined by a response of “quite a lot” or “extremely”).

Study Measures

Patient Demographics. Patient demographics included sex, age as a continuous variable, race/ethnicity (white vs nonwhite), marital status (married or living with partner vs not), and education (having a college degree vs no college degree).

Comorbid Conditions. Physical comorbidity was assessed by attempting to mimic the Charlson Comorbidity Index (CCI).¹⁵ The CCI is a measure of comorbidity burden that is calculated by weighting the presence of comorbidities by their severity. In this study, the presence of congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes mellitus, cancer, and human immunodeficiency virus was each weighted by its severity as outlined by Charlson et al¹⁵ and summed. The CCI was considered a continuous variable. Additional psychiatric comorbidity was assessed. Respondents were classified as having a psychiatric comorbid condition if any of the following conditions were experienced in the past 12 months: anxiety, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, phobias, post-traumatic stress disorder, and social anxiety disorder. In analysis, psychiatric condition was dummy coded as yes (1 point) or no (0 points).

Healthcare Resource Utilization. Healthcare resource utilization was assessed for the previous 6 months by obtaining information on emergency department (ED) services and hospitalizations. Patients were asked the following questions: “How many times have you been to the emergency room for your own medical condition in the past 6 months?” and “What is the total number of days you were hospitalized for your own medical condition in the past 6 months?”

Employment Status. Patients’ employment status was determined by asking: “What is your employment status?” Responses included “employed full-time,” “employed part-time,” “self-employed,” “not employed but looking for work,” “not employed and not looking for work,” “retired,” “on disability,” “student,” or “homemaker.” Patients reporting “employed full-time,” “employed part-time,” or “self-employed” were considered employed, while all others were considered not employed.

Absenteeism and Presenteeism Among Employed Patients. As part of the NHWS, indirect costs were assessed using the general health version of the Work Productivity and Activity Impairment (WPAI) questionnaire.¹⁶ The WPAI assesses absenteeism (the percentage of work time missed because of one’s health in the past 7 days), presenteeism (the percentage of impairment experienced while at work in the past 7 days because of one’s health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one’s health in the past 7 days). All employed respondents provided data for absenteeism, presenteeism, and overall work productivity loss (as those not employed could not answer questions about hours worked or hours missed from work). All respondents provided data for activity impairment.

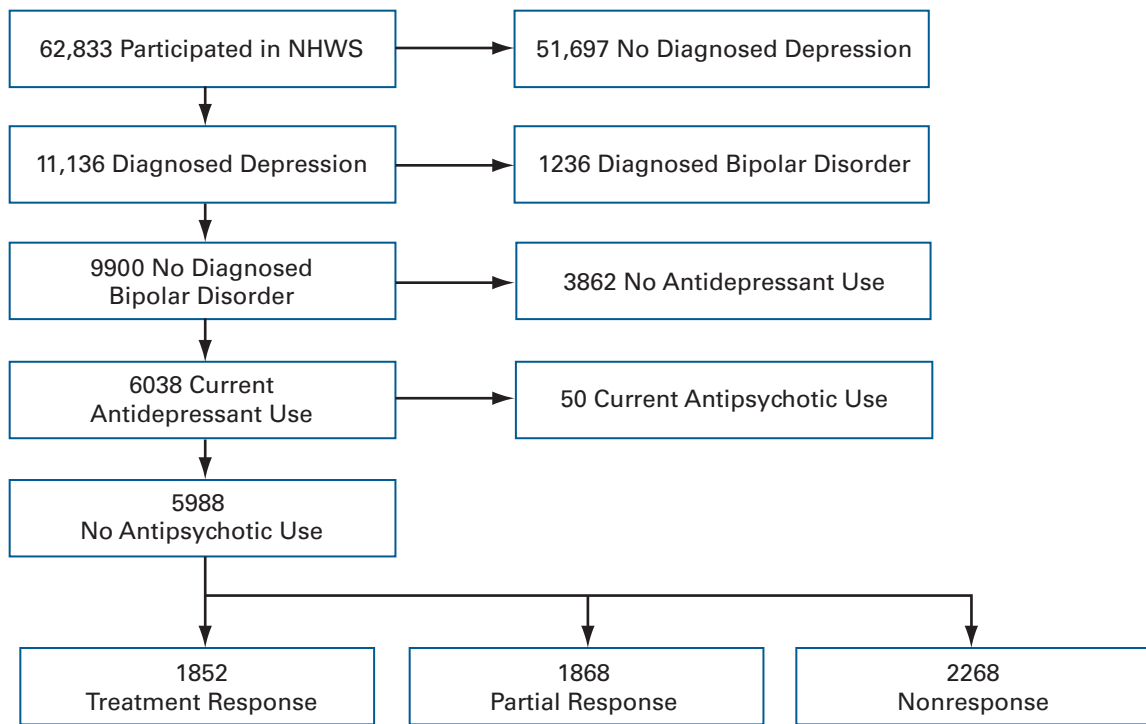
Absenteeism is calculated by dividing the number of work hours a patient missed in the past week because of his or her health by the total number of hours a patient could have worked (the number of hours he or she worked plus the number of hours missed because of health) and by converting this proportion into a percentage. For example, if a patient missed 5 hours and worked 35 hours, then absenteeism would be 12.5% ($5 \div [5 + 35] = 0.125$). Presenteeism was measured by a patient’s response to his or her level of impairment experienced while at work in the past 7 days (range, 0-10), which was then multiplied by 10 to create a percentage. If a patient reported his or her level of impairment as 2, this would be converted to a presenteeism level of 20.0%. Overall work productivity loss was measured by combining absenteeism and presenteeism. Activity impairment was measured by a patient’s response to his or her level of impairment experienced in daily activities in the past 7 days (range, 0-10), which was then multiplied by 10 to create a percentage. Only those who were employed had data for their levels of absenteeism, presenteeism, and overall work productivity loss. All patients had data for activity impairment.

Absenteeism, presenteeism, and overall work productivity loss were considered dichotomous variables (experiencing any impairment vs experiencing no impairment) and continuous variables. Activity impairment was assessed only as a continuous variable because 86.6% of respondents had some degree of activity impairment.

Statistical Analysis

Among patients having MDD treated with antidepressant therapy, we assessed demographics, comorbidity, work productivity loss, and healthcare resource utilization across the 3 treatment response categories. χ^2 Analysis was used to test for significant differences in categorical variables, and analysis of

■ **Figure.** Derivation of the Study Sample



NHWS indicates US National Health and Wellness Survey

variance was used to test for significant differences in continuous variables.

Regression models were fitted to assess the independent association of treatment response on healthcare resource utilization and on lost work productivity. Logistic regression models were used for the following dependent variables: ED use, hospitalization, and the dichotomized WPAI work productivity metrics of absenteeism, presenteeism, and overall work productivity loss. Linear regression models were used to assess the independent association of treatment response on the continuous WPAI metrics. Covariates for adjustment in all models included sex, age, race/ethnicity, marital status, college education, CCI, additional psychiatric comorbidity, and SF-8 physical component summary score.

Follow-up analyses were conducted to compare patients having TRD with all other patients having depressive symptoms in the NHWS to determine whether depressive symptoms or treatment failure was the primary cause of group differences. Similarly, a set of analyses was conducted to compare patients having TRD with patients having untreated depression who were still experiencing emotional problems. Logistic regression models were used for the following dependent variables: ED use, hospitalization, and the dichotomized WPAI work productivity metrics of absenteeism, presentee-

ism, and overall work productivity loss. Linear regression models were used to assess the independent association of treatment response on the continuous WPAI metrics. Covariates for adjustment in all models included sex, age, race/ethnicity, marital status, college education, medical and psychiatric comorbidities, and SF-8 physical component summary score.

RESULTS

Sample Characteristics

There were 62,833 participants in the 2006 US NHWS (Figure). Of these, 5,988 met the inclusion criteria for patients having MDD currently treated with antidepressant therapy and were included in the analyses. Within this cohort, 1,852 (30.9%) were categorized as treatment responders, 1,868 (31.2%) as partial responders, and 2,268 (37.9%) as nonresponders (Table 1). Partial responders and nonresponders were younger, more likely to be of nonwhite race/ethnicity, less likely to be married or living with a partner, and less likely to have a college degree than treatment responders. In addition, partial responders and nonresponders had greater comorbidity burden (as assessed by the CCI), more psychiatric comorbidities, and poorer physical health status.

■ **Table 1.** Characteristics of the Study Sample

Characteristic	Treatment Response			P ^a
	Responders (n = 1852)	Partial Responders (n = 1868)	Nonresponders (n = 2268)	
Female sex, %	66.1	60.5	64.9	<.01
Age, mean (SD), y	49.6 (14.0)	47.8 (14.0)	46.4 (13.1)	<.01
Nonwhite race/ethnicity, %	13.6	15.8	20.9	<.01
Married, %	60.9	59.9	57.1	.04
College education, %	38.3	33.6	26.7	<.01
Charlson Comorbidity Index, mean (SD)	0.6 (1.2)	0.8 (1.4)	0.8 (1.2)	<.01
Additional psychiatric comorbidity, %	46.5	65.4	79.5	<.01
SF-8 physical component summary score, mean (SD)	44.5 (10.3)	42.1 (11.2)	41.2 (11.8)	<.01

SF-8 indicates 8-Item Short Form Health Survey.
^aCalculated using χ^2 test and analysis of variance as appropriate.

Healthcare Resource Use

Before adjusting for demographic characteristics and comorbidity, partial response and nonresponse to treatment were associated with greater likelihood of ED utilization and hospitalization among patients having MDD treated with antidepressant therapy (Table 2). After adjusting for demographic characteristics, comorbidity, and SF-8 physical component summary score, the regression analysis showed that partial responders and nonresponders were 1.26 and 1.54 times, respectively, more likely to use the ED compared with treatment responders ($P < .01$ for both) (Table 3). Nonresponders were also significantly more likely to be hospitalized compared with partial responders (odds ratio [OR], 1.39; $P < .01$). Likelihood of hospitalization approached significance for partial responders compared with responders (OR, 1.23; $P = .05$).

Absenteeism and Presenteeism Among Employed Patients

Among patients having MDD treated with antidepressant therapy, partial response and nonresponse to treatment were associated with less likelihood of employment compared with treatment responders. Among patients who were employed full-time, partial response and nonresponse to treatment were associated with greater absenteeism, presenteeism, and overall work productivity loss (Table 2). Adjusting for demographic characteristics, comorbidity, and SF-8 physical component summary score, partial responders and nonresponders were significantly less likely to be employed (OR, 0.83; $P = .01$ and OR, 0.63; $P < .01$, respectively) compared with responders (Table 3). Among patients with MDD who were employed full-time, nonresponders to treatment were 2.37 times more likely to miss work (absenteeism) and 4.17 times more likely to experience impairment while working (presenteeism) than responders

to treatment ($P < .01$ for both). Partial responders were more likely to experience presenteeism (OR, 1.98; $P < .01$) than responders, but absenteeism was not significantly associated with partial response to treatment. Overall, partial responders and nonresponders were significantly more likely to experience significant work productivity loss (ORs, 1.42 and 1.99, respectively; $P < .01$ for both) than treatment responders.

Among all patients having MDD treated with antidepressant therapy, treatment nonresponse was also associated with impairment in daily activities. At a bivariate level, partial response and nonresponse were associated with greater activity impairment (Table 2). Adjusting for demographic characteristics, comorbidity, and SF-8 physical component summary score, partial responders and nonresponders had 9.9% and 21.4%, respectively ($P < .01$ for both) greater activity impairment than treatment responders (Table 3).

Comparing Patients With TRD vs Patients With Untreated Depression

Although significant differences were found between treatment responders versus partial responders or nonresponders, it remains unclear whether these effects were due to inadequate treatment response or the depressive symptoms themselves (because *nonresponse* was defined as having depressive symptoms while being treated). To address this alternative explanation, follow-up analyses were conducted comparing nonresponders with all other NHWS patients who were not being treated for depression but who were experiencing depressive symptoms (ie, 5292 patients who reported being bothered by emotional problems “quite a lot” or “extremely”). Controlling for demographic characteristics, comorbidity, and SF-8 physical component summary score, nonresponders were equally likely to visit the ED (OR, 1.08; $P = .21$) or to be hos-

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Table 2. Unadjusted Association of Treatment Response With Healthcare Resource Utilization and Work Productivity

Variable	Treatment Response, %			P ^a
	Responders (n = 1852)	Partial Responders (n = 1868)	Nonresponders (n = 2268)	
Emergency department use	17.5	25.0	31.1	<.01
Hospitalization	10.6	15.1	17.9	<.01
Employed	51.9	46.1	39.5	<.01
Activity impairment, mean (SD)	32.9 (29.3)	47.7 (29.0)	61.1 (27.9)	<.01
	Among Full-Time Employed			
	(n = 707)	(n = 597)	(n = 603)	
Absenteeism				
Any	22.2	29.6	42.5	<.01
Mean (SD) ^b	5.2 (15.0)	7.4 (16.9)	13.7 (25.6)	<.01
Presenteeism				
Any	62.4	77.8	85.6	<.01
Mean (SD) ^b	20.9 (23.7)	30.7 (25.5)	41.3 (27.1)	<.01
Overall work productivity loss				
Any	44.30	54.90	63.60	<.01
Mean (SD) ^b	17.0 (25.6)	24.0 (28.3)	34.9 (34.3)	<.01

^aCalculated using χ^2 test and analysis of variance as appropriate.

^bBecause impairment was measured as a percentage for each patient, the mean (SD) represents the mean percentage of impairment and the SD of that impairment.

pitalized (OR, 0.98; $P = .71$) relative to all other patients experiencing depressive symptoms. However, nonresponders were significantly less likely to be employed (OR, 0.78; $P < .001$) and were significantly more likely to experience some level of work impairment ($>0\%$) as a result of absenteeism (OR, 1.24), presenteeism (OR, 1.46), and overall work productivity loss (OR, 1.28) ($P < .001$ for all) relative to all other patients experiencing depressive symptoms. Differences in the mean levels of absenteeism were not significantly different between nonresponders and all other patients experiencing depressive symptoms ($\beta = 1.52$, $P = .07$). Nonresponders experienced significantly greater mean levels of presenteeism ($\beta = 3.43$, $P < .001$), overall work productivity loss ($\beta = 3.16$, $P = .008$), and activity impairment ($\beta = 4.79$, $P < .001$) relative to all other patients experiencing depressive symptoms.

An additional follow-up analysis was conducted to compare nonresponders with 3173 patients who were experiencing depression and depressive symptoms (being bothered by emotional problems “quite a lot” or “extremely”) but were not treated for their depression. Controlling for demographic characteristics, comorbidity, and SF-8 physical component summary score, nonresponders were marginally more likely to visit the ED (OR, 1.13; $P = .07$) but were no more likely to be hospitalized (OR, 1.10; $P = .23$) relative to patients not being

treated for depression and experiencing depressive symptoms. However, nonresponders were significantly less likely to be employed (OR, 0.87; $P = .02$). Nonresponders were also marginally more likely to experience some level of absenteeism ($>0\%$) (OR, 1.14; $P = .05$) and overall work productivity loss (OR, 1.15; $P = .08$) and reported significantly higher mean levels of activity impairment ($\beta = 2.54$, $P < .001$). Conversely, nonresponders were no more likely to experience some level of presenteeism ($>0\%$) (OR, 1.08; $P = .53$).

DISCUSSION

Among a nationwide sample of patients with MDD currently receiving treatment with antidepressant medication, these results demonstrate that almost 70% did not respond adequately to therapy. The data are consistent with the clinical literature.^{4,6-8} Among partial responders and nonresponders, there were significant increases in direct and indirect economic costs.

In the present study, partial response or nonresponse to treatment was associated with substantial direct economic effect, as there was a significantly greater likelihood of ED use among both groups and a significantly increased hospitalization rate among the nonresponders compared with the

■ **Table 3.** Adjusted Association of Treatment Response With Healthcare Resource Utilization and Work Productivity^a

Variable	Treatment Response			
	Partial Responders		Nonresponders	
	OR (95% CI)	P	OR (95% CI)	P
Emergency department use	1.26 (1.07 to 1.49)	<.01	1.54 (1.31 to 1.81)	<.01
Hospitalization	1.23 (1.00 to 1.51)	.05	1.39 (1.14 to 1.70)	<.01
Employed	0.83 (0.72 to 0.96)	.01	0.63 (0.54 to 0.72)	<.01
Activity impairment, % ^b	9.91 (8.57 to 11.24)	<.01	21.39 (20.07 to 22.72)	<.01
Among Full-Time Employed				
Any absenteeism	1.23 (0.97 to 1.56)	.08	2.37 (1.89 to 2.99)	<.01
Any presenteeism	1.98 (1.57 to 2.50)	<.01	4.17 (3.19 to 5.45)	<.01
Any overall work productivity loss	1.42 (1.17 to 1.73)	<.01	1.99 (1.62 to 2.44)	<.01
Absenteeism ^b	1.17 (-0.89 to 3.23)	.27	7.49 ^b (5.38 to 9.60)	<.01
Presenteeism ^b	7.78 (5.39 to 10.18)	<.01	18.26 ^b (15.78 to 20.73)	<.01
Work productivity loss ^b	5.44 (2.45 to 8.43)	<.01	15.85 ^b (12.79 to 18.92)	<.01

CI indicates confidence interval; OR, odds ratio.
^aAdjusting for age, sex, race/ethnicity, marital status, college education, physical comorbidity, additional psychiatric comorbidity, and 8-Item Short Form Health Survey physical component summary score using logistic and linear regression analyses as appropriate.
^bHealthcare resource utilization and dichotomized impairment variables were analyzed using logistic regression analysis, while continuous impairment variables were analyzed using multiple regression analysis. Responders served as the reference category for each OR and regression estimate.

responders. This increased healthcare utilization will likely lead to increased costs, which is consistent with previous research that reported greater cost of care among partial responders and nonresponders. A randomized trial by Simon et al¹⁷ in 7 primary care clinics demonstrated that total annual healthcare costs for nonresponders were \$620 higher than those for partial responders and \$1266 higher than those for patients having MDD with symptom remission. In addition, Corey-Lisle et al¹⁸ applied a treatment algorithm to a claims database to estimate whether patients with MDD were treatment resistant (“TRD likely”) or not (“TRD unlikely”) and found that TRD-likely patients in a Fortune 100 manufacturing company used almost twice as many medical services and had more than twice the annual medical costs compared with TRD-unlikely patients (\$10,954 vs \$5025).

Analysis of indirect costs associated with MDD also showed significant economic effect. Presenteeism, the amount of lost productivity due to impairment from illness, is a serious issue facing employers. There was less likelihood of employment among partial responders and nonresponders; however, among those who were employed full-time, nonresponders experienced significantly greater lost work productivity than responders. For example, nonresponders were more than 4 times as likely as responders and twice as likely as partial responders to experience presenteeism. Partial responders experienced increased absenteeism and significantly greater presenteeism

than responders. In addition, partial responders and nonresponders had significant activity impairment.

These results are consistent with previous studies demonstrating the negative effect of partial response and nonresponse to depression treatment on work productivity. Stewart et al¹⁹ found more health-related lost productive work time among nonresponders (8.4 h/wk) compared with partial responders (3.3-5.3 h/wk) and employees having MDD with symptom remission (1.5 h/wk) in a nationwide study of the US employed population. A study²⁰ examining psychosocial functioning in 92 patients with TRD revealed mild-to-moderate work impairment and poor involvement in recreational activities.

Because TRD is defined by the level of depressive symptoms, one explanation for the findings herein is that the depressive symptoms (and not the lack of treatment response) are the source of the observed effects. However, our follow-up analyses revealed that patients with TRD had greater work-related impairment than patients with untreated depressive symptoms (a measure of indirect costs). Patients with TRD also had increased activity impairment and were marginally more likely to have absenteeism and overall work productivity loss than patients with untreated depression and depressive symptoms. Collectively, the findings of these analyses suggest that lack of treatment response is a predictor of worse outcome beyond that of depressive symptoms alone. However, no differences were found between these groups in resource

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use, suggesting that lack of treatment response may not be independently associated with direct costs. Another possible explanation is that medication adverse effects experienced by nonresponders contribute to worse outcomes in that group relative to those who were untreated. Further research is necessary to test these alternative hypotheses.

Limitations of this study include the fact that it was a cross-sectional analysis based on the results of a self-reported patient survey. Data were not validated to assess the severity of depression, which may significantly affect work productivity, daily activities, and healthcare resource utilization. Furthermore, self-reported survey data have the potential for recall bias. In the NHWS, WPAI metrics were recalled for the past 7 days, SF-8 items were recalled for the past 4 weeks, and healthcare resource use was recalled for the past 6 months. The accuracy of the WPAI and the SF-8 has been well validated for their recall periods. Healthcare resource use is evaluated for a longer period, but because hospitalizations and ED visits are noteworthy events for an individual, recall bias may be minimal. Nevertheless, it is possible that individuals who had TRD recalled resource use differently than those who did not have TRD. In addition, it is unclear from the data whether patients were receiving therapeutic dosages of their depression medication and whether they had been using their medication long enough to be considered adequately treated. This lack of information may have caused additional error in the definition of the TRD group. For example, patients who may not have been taking their medication for a sufficient period or who received an insufficient dosage may have been erroneously considered as having TRD.

Cross-sectional analysis examines the relationship between different variables at a point in time and is at best correlational. This study may inform future hypothesis-testing studies that are designed to establish causality and that use a combination of disease-specific and general measures. Finally, the study was conducted on the Internet, which may limit the generalizability of the results because of sample selection bias. According to the US Census Bureau,²¹ approximately 70% of adults in the United States had Internet access in 2006, but it is unclear what proportion of patients with MDD have Internet access.

In summary, while remission is the goal for individuals with MDD,³ most patients in the present study experienced partial response or nonresponse to their antidepressant medication, which was associated with increased healthcare resource utilization, less likelihood of employment, and greater work productivity loss for those who were employed. Results of follow-up analyses suggest that it was lack of treatment response (and not just depressive symptoms) that was associated with work impairment and indirect costs (although this was not

the case with resource use and direct costs). Based on these data, it is reasonable to hypothesize that increasing the response rates to treatment will have positive economic benefits by reducing the indirect costs due to reduced productivity.²²

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