Association Between Cognitive Function and Health Care Costs 3 Months and 6 Months After Initiating Antidepressant Medication for Depressive Disorders

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ABSTRACT

BACKGROUND: Major depressive disorder is one of the most common and disabling mental health disorders and is associated with substantial costs in terms of direct health care utilization and workplace productivity. Cognitive dysfunction, which alone substantially increases health care costs, is commonly associated with major depressive disorder. However, the health care costs of cognitive dysfunction in the context of depressive disorder are unknown. Recovery from mood symptoms is not always associated with resolution of cognitive dysfunction. Thus, cognitive dysfunction may contribute to health care burden even with successful antidepressant therapy.

OBJECTIVE: To compare health care utilization and costs for patients with a depressive disorder with and without cognitive dysfunction, at 3 and 6 months after initiation of antidepressant medication.

METHODS: This was an observational study, combining a cross-sectional patient survey, administered during a telephone interview, with health care claims data from a large, geographically diverse U.S. health plan. Included patients had at least 1 pharmacy claim for an antidepressant medication between August 1 and September 30, 2012, and no claim for any antidepressant during the 6 months prior to the index date. In addition to other criteria assessed in the claims data, patients confirmed a diagnosis of depression or major depressive disorder and the absence of any exclusionary neurological diagnoses possibly associated with cognitive impairment. Eligible patients were administered validated cognitive function assessments of verbal episodic memory (Hopkins Verbal Learning Test-Revised, Delayed and Total); attention (Digit Span Forward Maximum Sequence Length); working memory (Digit Span Backward Maximum Sequence Length); and executive function (D-KEFS-Letter Fluency Test). Based on comparison of scores with normative data, patients were assigned to cognitive dysfunction or cognitive normal cohorts. All-cause (all diagnoses) and depressive disorder-related health care utilization and costs (all from a payer perspective) were assessed 6 months prior (baseline) to antidepressant initiation and 3 months and 6 months after (follow-up) initiation of antidepressant medication. Health care utilization and costs included ambulatory (office and hospital outpatient), emergency room, inpatient hospital, pharmacy, other medical (e.g., laboratory and diagnostics), and total (all categories combined). All-cause and depressive disorder-related total costs during the 3- and 6-month follow-up periods were modeled with generalized linear modeling with gamma distribution and log link, while adjusting for potential confounders (age, race, gender, education, employment, and comorbidities).

RESULTS: Of the 13,537 patients who were mailed an invitation, 824 (6%) were eligible and agreed to participate. Of these, 563 patients provided informed consent, completed the interview, maintained eligibility, and were included in the 3-month calculations. Among these, 255 (45%) were classified as having cognitive dysfunction. Mean patient age was 41.3 (± 12.5) years; 80% were female. Most patients were white and employed.

More patients in the cognitive normal cohort were white ($P < 0.001$) and employed full time ($P = 0.029$), had higher education attainment ($P < 0.001$), and had fewer comorbidities ($P = 0.007$) than those in the cognitive dysfunction cohort. Over the first 3 months, patients with cognitive dysfunction had higher adjusted all-cause costs (\$3,309 vs. \$2,157, $P = 0.002$) and higher adjusted depressive disorder-related costs (\$718 vs. \$406, $P < 0.001$) than patients without cognitive dysfunction. At 6 months, data from 4 patients were removed from the analysis because of exclusionary diagnoses. Over 6 months, patients with cognitive dysfunction had higher adjusted all-cause costs (\$4,793) than patients without cognitive dysfunction (\$3,683, $P = 0.034$). Over 6 months, depressive disorder-related costs did not significantly differ between patients with (\$771) and without cognitive dysfunction (\$594, $P = 0.071$). The main drivers of all-cause costs were office visits, outpatient hospital visits, and inpatient costs, and the main driver of depressive disorder-related costs was inpatient costs.

CONCLUSIONS: Cognitive dysfunction was associated with higher adjusted all-cause and depressive disorder-related costs 3 months after initiation of an antidepressant medication. This difference persisted for all-cause costs through 6 months. Identification and treatment of cognitive dysfunction in patients with depressive disorder might reduce health care costs.

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What is already known about this subject

- Major depressive disorder has an estimated lifetime prevalence of 10%-20% in the United States and imposes significant economic and societal consequences in terms of direct medical care costs, associated morbidity and mortality, and productivity costs.
- Cognitive dysfunction, which is commonly associated with major depressive disorder, may persist even after resolution of other symptoms of depression.
- By itself, a diagnosis of cognitive dysfunction is associated with up to triple the health care costs of persons without such a diagnosis. However, costs related to cognitive dysfunction in the context of depression have not been reported.

What this study adds

- Using data from a large U.S. health plan, we analyzed health care utilization and costs for patients with a depressive disorder, with and without cognitive dysfunction, for 3 and 6 months following the initiation of antidepressant medication.

What this study adds (*continued*)

- Patients with cognitive dysfunction had significantly more all-cause outpatient hospital visits during the first 3 months after initiating antidepressant medication. At 6 months, patients with cognitive dysfunction had significantly more all-cause emergency room visits and depressive disorder-related outpatient visits.
- Relative to patients without cognitive dysfunction, patients with cognitive dysfunction had significantly higher all-cause and depressive disorder-related health care costs 3 months following initiation of an antidepressant and higher all-cause costs 6 months following initiation of an antidepressant.

Major depressive disorder (MDD) is one of the most common and disabling mental health disorders, with a lifetime prevalence estimated at 10%-20% in the United States and with higher rates for women than men.¹⁻³ Depression has significant economic and societal consequences. In 2000, the estimated costs of depression were \$83.1 billion, including \$26.1 billion in direct medical costs and \$51.5 billion in workplace productivity costs.⁴ Per patient annual direct medical costs of depression up to \$2,500 have been reported.⁵ As a major health problem associated with gradual and often incomplete recovery, MDD imposes significant limitations on functioning and well-being, raises the risk of mortality due to medical illness, and increases utilization of health services and associated costs to society.⁶

Cognitive dysfunction is commonly associated with MDD and is characterized by “difficulty thinking, concentrating, or making decisions,” which is part of the MDD diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.⁷ Resolution of depression is not always associated with recovery from cognitive dysfunction, and there is increasing evidence of persistent cognitive dysfunction even after resolution of depressive symptoms.⁸⁻¹⁰ Thus, cognitive dysfunction may contribute to health care burden even after successful treatment of other symptoms of MDD.

Cognitive dysfunction by itself is associated with higher health care costs. In fact, people diagnosed with dementia, an extreme form of cognitive dysfunction, have experienced triple the health care costs of persons with no such diagnosis.¹¹ The costs related to cognitive dysfunction in the context of depression have not been reported. The objectives of this study were to compare health care utilization and costs from a payer perspective for patients with a depressive disorder, with and without cognitive dysfunction, for 3 months and 6 months after the start of antidepressant medication. These results will be of importance to health care providers and payers involved with the treatment of patients with a depressive disorder experiencing cognitive dysfunction.

Methods

Design

This was a real-world, observational study, combining a cross-sectional patient survey administered during a telephone interview with patients' health care claims data from the Optum Research Database (ORD). The ORD contains data for approximately 33.9 million patients with commercial insurance, representing all U.S. geographic census regions.¹²

Pharmacy claims data were used to identify patients initiating an antidepressant medication between August 1 and September 30, 2012 (the date of the first antidepressant pharmacy claim is the index date). In November 2012, identified patients were mailed an invitation to participate in the study. A telephone interview was conducted for each participant between November 14 and December 28, 2012. Cognitive function assessments and other patient-reported outcomes were collected during the telephone interviews. Pharmacy and medical claims data were used to calculate health care costs in the 6-month period pre-index date (baseline period) and the 3- and 6-month periods post-index date (follow-up periods).

Patients

The study protocol received a waiver of authorization and ethics approval from the New England Institutional Review Board, and all patients completed informed consent and health information release forms. Patients had at least 1 pharmacy claim for an antidepressant between August 1 and September 30, 2012, and no claim for any antidepressant during the 6 months prior to the index date. Medical claims for recent depressive episodes were unavailable at the time of patient identification due to a 6-month lag required for complete medical claims; therefore, each patient confirmed a diagnosis of depression or MDD and the absence of any exclusionary neurological diagnoses possibly associated with cognitive impairment (see Appendices A-D, available in online article, for complete inclusion/exclusion criteria).

Demographics and Clinical Characteristics

Claims data from the baseline period were used to obtain age, gender, and geographic region; to identify comorbid conditions as defined in the Agency for Healthcare Research and Quality Clinical Classification Software; and to calculate the Quan-Charlson Comorbidity Index score based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes (a measure of comorbidity burden).^{13,14}

Eligible patients interviewed by telephone provided race and ethnicity, employment status, occupation, and highest education level achieved. Patient-reported outcome assessments measuring depression severity, disability, self-reported cognitive functioning, and health-related quality of life were also administered, and these results are reported separately.¹⁵

Assessment of Cognitive Function

Each patient completed a structured assessment of objectively measured cognitive function measuring 4 domains: verbal episodic memory (Hopkins Verbal Learning Test-Revised [HVLRT-R] Delayed and Total); attention (Digit Span Forward [DSF] Maximum Sequence Length); working memory (Digit Span Backward [DSB] Maximum Sequence Length); and executive function (D-KEFS-Letter Fluency Test).¹⁶⁻¹⁸ These tests were chosen because they represent the domains found to be most impaired in acute depression and have been shown to be sensitive to depression-related cognitive dysfunction.¹⁹⁻²¹ Performance on each test was compared with published age- and gender-stratified normative data and then used to classify each patient's cognition as either normal or dysfunctional.¹⁶⁻¹⁸ Patients were classified as having "cognitive dysfunction" if they met at least 1 of 2 criteria: (1) two or more test scores 1.5 standard deviations (SD) or more below the normative mean, or (2) three or more test scores 1.0 SD or more below the normative mean.²² Patients not meeting either of these criteria were classified as "cognitive normal." See Figure 1 for cohort assignment.

Health Care Utilization and Costs

Health care utilization and costs from a payer perspective were calculated from pharmacy and medical claims 6 months prior (baseline) to antidepressant initiation, 3 months after initiation of antidepressant medication (3-month follow-up), and 6 months (including the 3-month follow-up) after initiation of antidepressant medication (6-month follow-up). Health care costs represent the sum of health plan and patient-paid amounts and were classified as follows: office visits, outpatient hospital visits, emergency room, inpatient, other medical, pharmacy, and total costs (combining all of these categories). An example of "other medical" costs would be independent laboratory and diagnostic costs. "All-cause" costs included the cost of all health care utilization consumed during the study period, regardless of the diagnosis, and "depressive disorder-related" costs included medical claims having a primary or nonprimary diagnosis code for, or relating to, depressive disorder (ICD-9-CM codes 296.82 [atypical depressive disorder], 296.2x [major depressive disorder, single episode], 296.3x [major depressive disorder, recurrent episode], 311 [depressive disorder, not elsewhere classified]) and associated pharmacy claims (see Appendices B and E, available in online article).

Statistical Analyses

Chi-square and t-tests were used to compare demographic characteristics and health care utilization between the cognitive dysfunction and cognitive normal cohorts for categorical and continuous variables, respectively. Two-sided t-tests were used to compare health care costs between the 2 cohorts. We used a generalized linear model (GLM) with gamma distribution and log link to assess the relationship between cognitive function

and total all-cause costs, controlling for potential confounders of performance on neuropsychological tests (level of education, race, gender, age, level of employment, Quan-Charlson comorbidity score, and mental health-related comorbidities). Because health care costs are often skewed, estimated cost measures were modeled using Manning and Mullahy's formulation.²³ This method avoids potential difficulties introduced by transformation and retransformation of the dependent variable.²⁴ Coefficients from a GLM are estimated cost ratios.

Adjusted costs for all-cause health care utilization were estimated from the gamma models for 3- and 6-month follow-up periods. The same approach was used to assess the relationship between cognitive function and depressive disorder-related costs, controlling for the same potential confounders.

A logistic regression analysis in which presence of nonzero baseline costs (measured as a binomial) as the dependent variable was performed with a single independent (predictor) variable as presence of cognitive dysfunction (measured as a binomial). Logistic regression assesses the relationship between a binomial (or categorical) dependent variable and a set of independent variables. This model was used because the binomial outcome variable violates assumptions of ordinary least squares regression. A GLM with log link and gamma distribution assessed the relationship between cognitive dysfunction (as a single, binomial predictor variable) and nonzero baseline costs.

Results

Study Sample

Of the 13,537 patients who were mailed an invitation to participate in the study, 824 (6%) were eligible and agreed to participate (Figure 1). Of this number, 563 patients completed the informed consent process, completed a telephone interview, maintained eligibility, and were included in the calculation of 3-month health care utilization and costs. Four patients were removed from the calculation of 6-month costs because they had an exclusionary diagnosis of bipolar disorder during the 6-month follow-up period, leaving 559 patients in the 6-month analysis.

Demographics

Of the 563 patients in the 3-month follow-up analysis, 255 (45%) met the criteria for cognitive dysfunction. The mean patient age was 41.3 (SD=12.5) years, and 80% were female. Most patients were white and employed. More patients in the cognitive normal cohort were white and employed full time, had higher education, and had fewer comorbidities compared with patients in the cognitive dysfunction cohort. Demographic details are shown in Table 1.

Costs at Baseline

In the 6 months prior to antidepressant initiation (baseline), the unadjusted all-cause costs were \$6,431 for the cognitive dysfunction cohort compared with \$3,953 for the cognitive normal cohort

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FIGURE 1 Study Sample Selection Flowchart

^aBupropion, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, desvenlafaxine, duloxetine, venlafaxine, mirtazapine, nefazodone, trazodone, or vilazodone. This is also referred to as the index AD, that is, the AD received on the index date.

^bSchizophrenia, bipolar disorder, Alzheimer's disease, epilepsy disorder, Huntington's disease, Parkinson's disease, or multiple sclerosis.

^cMedication for schizophrenia, bipolar disorder, Alzheimer's disease, epilepsy disorder, Huntington's disease, Parkinson's disease, or multiple sclerosis.

^dClinical Classification Software designations for substance abuse, coma, stupor, brain damage, hereditary and degenerative nervous system conditions, or delirium/dementia.

^eThe claims database is updated periodically, and some patients' exclusionary diagnoses were not identified in the claims database until after interviews were conducted. AD=antidepressant; DD=depressive disorder; SD=standard deviation.

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TABLE 1 Demographics and Clinical Characteristics by Cohort

Characteristics	Total Sample (N = 563)		Cognitive Normal (n = 308)		Cognitive Dysfunction (n = 255)		P Value
Age, mean (SD), years	41.3	(12.5)	41.9	(12.5)	40.5	(12.5)	0.191
Female sex, n (%)	449	(79.8)	250	(81.2)	199	(78.0)	0.358
Region, n (%)							
South	266	(47.3)	140	(45.5)	126	(49.4)	0.778
Midwest	184	(32.7)	106	(34.4)	78	(30.6)	
West	86	(15.3)	47	(15.3)	39	(15.3)	
Northeast	27	(4.8)	15	(4.9)	12	(4.7)	
Race, n (%) ^a							
White	516	(92.3)	293	(95.8)	223	(88.1)	<0.001
Black or African American	29	(5.2)	13	(4.3)	16	(6.3)	0.271
American Indian	10	(1.8)	6	(2.0)	4	(1.6)	0.736
Asian	6	(1.1)	3	(1.0)	3	(1.2)	0.815
Native Hawaiian or other Pacific Islander	2	(0.4)	0	(0.0)	2	(0.8)	0.119
Other	12	(2.2)	4	(1.3)	8	(3.2)	0.132
Hispanic/Latino	36	(6.4)	19	(6.2)	17	(6.7)	0.810
Employment status, n (%) ^a							
Employed full time	365	(64.8)	212	(68.8)	153	(60.0)	0.029
Employed part time	105	(18.7)	51	(16.6)	54	(21.2)	0.161
Homemaker	82	(14.6)	48	(15.6)	34	(13.3)	0.451
Student	64	(11.4)	39	(12.7)	25	(9.8)	0.288
Unemployed	43	(7.6)	21	(6.8)	22	(8.6)	0.421
Other	15	(2.7)	11	(3.6)	4	(1.6)	0.142
Retired	12	(2.1)	7	(2.3)	5	(2.0)	0.799
Education, n (%)							
Graduate school	84	(14.9)	60	(19.5)	24	(9.4)	<0.001
College graduate	156	(27.7)	98	(31.8)	58	(22.8)	
Two-year degree	83	(14.7)	46	(14.9)	37	(14.5)	
Some college, but no degree	148	(26.3)	72	(23.4)	76	(29.8)	
High school or equivalent	83	(14.7)	32	(10.4)	51	(20.0)	
Some high school	8	(1.4)	0	(0.0)	8	(3.1)	
Less than high school	1	(0.2)	0	(0.0)	1	(0.4)	
Quan-Charlson score, mean (SD)	0.24	(0.77)	0.16	(0.59)	0.34	(0.93)	0.007
Depressive disorder duration, mean (SD), days ^b	2,406.8	(2,790.3)	2,486.8	(2,805.5)	2,304.5	(2,774.7)	0.502
Time to survey, n (%) ^c							
61-90 days	118	(21.2)	74	(24.3)	44	(17.5)	0.035
91-120 days	302	(54.3)	151	(49.5)	151	(60.2)	
> 120 days	136	(24.5)	80	(26.2)	56	(22.3)	

^aPatients may report more than 1 category.

^bCalculated from patient-reported date of depression diagnosis.

^cTime between index antidepressant fill and survey.

SD = standard deviation.

($P=0.067$; Table 2). The main cost drivers for all-cause costs were office visits, outpatient hospital visits, and inpatient costs. The mean 6-month baseline unadjusted depressive disorder-related total costs were \$782 for the cognitive dysfunction cohort compared with \$108 for the cognitive normal cohort ($P=0.133$). The main cost driver for the depressive disorder-related costs in the cognitive dysfunction cohort was inpatient costs of \$702 for 4 patients with hospitalizations. There were no inpatient costs in the cognitive normal cohort. The results from the multiple logistic regression models comparing the proportion of patients

with costs to patients without costs found no significant difference between the 2 cohorts for unadjusted all-cause ($P=0.503$) or unadjusted depressive disorder-related costs ($P=0.557$).

The gamma models with a log link that compared costs for all patients, including patients with no costs, found a significant difference between the 2 cohorts for unadjusted all-cause ($P<0.001$) and unadjusted depressive disorder-related costs ($P<0.001$). When inpatient costs were removed from the gamma model, the difference in unadjusted depressive disorder-related costs between the cohorts was no longer significant.

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TABLE 2 Mean Unadjusted and Adjusted Total Costs over Baseline, 3 Months and 6 Months by Cohort

Total Costs	Total Sample (\$)	Cognitive Dysfunction (\$)	Cognitive Normal (\$)	Difference (CD-CN) (\$)	Gamma Model P Value
6-month baseline					
Unadjusted	n = 564	n = 309	n = 255		
All-cause	5,074	6,431	3,953	2,478 ^a	0.067
Depressive disorder-related	412	782	108	674 ^a	0.133
3-month follow-up					
Unadjusted	n = 563	n = 308	n = 255		
All-cause	3,053	3,948	2,312	1,636	0.113
Depressive disorder-related	739	951	564	387	0.536
Adjusted		n = 306	n = 253		
All-cause		3,309	2,157	1,152	0.002
Depressive disorder-related		718	406	312	<0.001
6-month follow-up					
Unadjusted	n = 559	n = 307	n = 252		
All-cause	5,186	6,707	3,938	2,769	0.040
Depressive disorder-related	1,010	1,316	759	557	0.387
Adjusted		n = 305	n = 250		
All-cause		4,793	3,683	1,110	0.034
Depressive disorder-related		771	594	177	0.071

^aFor the gamma model (non/zero baseline costs), P values <0.001. Logistic model P values were nonsignificant for all-cause costs (P=0.503) and depressive disorder-related costs (P=0.557).

CD=cognitive dysfunction cohort; CN=cognitive normal cohort.

Follow-up Health Care Utilization

Table 3 provides the number of patients with at least 1 occurrence of health care utilization as well as the mean number per patient, including those patients with no use of health care utilization. Significantly more patients with cognitive dysfunction than without had all-cause outpatient hospital visits over the first 3 months after antidepressant initiation (32.6% vs. 24.7%, $P=0.039$; Table 3). Over 6 months, 46.8% of patients with cognitive dysfunction had all-cause outpatient hospital visits compared with 40.1% of patients without cognitive dysfunction; however, the difference between cohorts was no longer statistically significant ($P=0.108$). Over 6 months, more patients with cognitive dysfunction had an all-cause emergency room visit compared with patients without cognitive dysfunction (29.0% vs. 19.5%, $P=0.009$). Over that span, significantly more patients with cognitive dysfunction than without had an outpatient visit for depressive disorder (8.3% vs. 4.2%, $P=0.044$).

Follow-up All-Cause Costs

At 3 months, the difference in unadjusted all-cause total costs was not statistically significant ($P=0.113$; Tables 2 and 4). By 6 months, however, the unadjusted all-cause total costs were significantly higher (\$6,707) for patients with cognitive dysfunction compared with those without cognitive dysfunction (\$3,938, $P=0.040$; Tables 2 and 4). For both follow-up periods, the largest cost drivers were office and outpatient visits, which accounted for half of total costs, followed by inpatient costs,

which accounted for one-quarter of total costs. The difference between the 2 cohorts was significantly higher ($P=0.012$ and 0.011) for outpatient hospital visits in the cognitive dysfunction cohort for the 3- and 6-month periods and emergency room visits ($P=0.047$) for the 6-month period. Median costs were similar across the 2 cohorts for the 3-month and 6-month total costs and cost components (i.e., office, outpatient hospital, emergency room, inpatient, other medical, and pharmacy).

The adjusted gamma model yielded significant differences in mean all-cause costs (Table 2). At 3 months, patients with cognitive dysfunction had higher adjusted all-cause costs compared with patients in the cognitive normal cohort (\$3,309 vs. \$2,157, $P=0.002$). Patients with cognitive dysfunction also had higher 6-month adjusted all-cause costs than those without cognitive dysfunction (\$4,793 vs. \$3,683, $P=0.034$). Gamma models yielded cost ratios (see Appendix F, available in online article) for all-cause costs at 1.53 times higher (95% confidence interval [CI]=1.17-2.02, $P=0.002$) for patients with cognitive dysfunction than for patients without cognitive dysfunction at 3 months. In addition, baseline Quan-Charlson score >0 and full-time employment were significantly and positively associated with all-cause costs during the 3-month follow-up period. The cost ratio at 6 months for all-cause costs was 1.30 times higher (95% CI=1.02-1.66, $P=0.034$) for the cognitive dysfunction cohort than the cognitive normal cohort. Baseline Quan-Charlson score >0 was significantly and positively associated with all-cause costs during the 6-month follow-up period.

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TABLE 3 All-Cause and Depressive Disorder-Related Health Care Utilization over 3 Months and 6 Months by Cohort

	All-Cause Utilization		P Value	Depressive Disorder-Related Utilization		P Value
	Cognitive Normal (n = 308)	Cognitive Dysfunction (n = 255)		Cognitive Normal (n = 308)	Cognitive Dysfunction (n = 255)	
3 Months						
Ambulatory visit, n (%)	273 (88.6)	222 (87.1)	0.567	97 (31.5)	82 (32.2)	0.866
Office visit	271 (88.0)	219 (85.9)	0.459	94 (30.5)	79 (31.0)	0.906
Outpatient hospital visit	76 (24.7)	83 (32.6)	0.039	11 (3.6)	12 (4.7)	0.498
ER visit, n (%)	42 (13.6)	45 (17.7)	0.190	3 (1.0)	8 (3.1)	0.065
Inpatient hospital stay, n (%)	12 (3.9)	6 (2.4)	0.300	6 (2.0)	3 (1.2)	0.467
Prescriptions, n (%)	306 (99.4)	251 (98.4)	0.290	305 (99.0)	250 (98.0)	0.325
Ambulatory visit, mean (SD)	4.47 (4.7)	5.05 (5.7)	0.198	0.73 (1.7)	0.71 (1.4)	0.892
Office visit	3.62 (3.7)	3.80 (4.2)	0.596	0.66 (1.5)	0.65 (1.3)	0.947
Outpatient hospital visit	0.87 (2.1)	1.25 (2.7)	0.068	0.07 (0.4)	0.06 (0.3)	0.756
ER visit, mean (SD)	0.24 (0.8)	0.36 (1.2)	0.191	0.02 (0.2)	0.07 (0.5)	0.063
Inpatient hospital stay, mean (SD)	0.04 (0.2)	0.04 (0.3)	0.990	0.02 (0.1)	0.02 (0.2)	0.758
Length of hospital stay, days, mean (SD)	0.22 (1.7)	0.36 (3.3)	0.536	0.13 (1.6)	0.17 (2.2)	0.830
Prescriptions, mean (SD)	7.07 (5.0)	7.84 (5.8)	0.096	3.17 (1.8)	3.33 (2.2)	0.352
6 Months	All-Cause Utilization		P Value	Depressive Disorder-Related Utilization		P Value
	Cognitive Normal (n = 307)	Cognitive Dysfunction (n = 252)		Cognitive Normal (n = 307)	Cognitive Dysfunction (n = 252)	
Ambulatory visit, n (%)	290 (94.5)	238 (94.4)	0.993	117 (38.1)	96 (38.1)	0.997
Office visit	289 (94.1)	235 (93.3)	0.668	114 (37.1)	88 (35.9)	0.588
Outpatient hospital visit	123 (40.1)	118 (46.8)	0.108	13 (4.2)	21 (8.3)	0.044
ER visit, n (%)	60 (19.5)	73 (29.0)	0.009	3 (1.0)	7 (2.8)	0.110
Inpatient hospital stay, n (%)	17 (5.5)	15 (5.6)	0.993	8 (2.6)	5 (2.0)	0.627
Prescriptions, n (%)	305 (99.4)	249 (98.8)	0.501	304 (99.0)	249 (98.8)	0.808
Ambulatory visit, mean (SD)	7.64 (8.1)	8.75 (10.6)	0.174	1.03 (2.4)	1.02 (2.2)	0.958
Office visit	6.04 (6.4)	6.43 (8.2)	0.538	0.95 (2.2)	0.92 (2.1)	0.882
Outpatient hospital visit	1.64 (3.5)	2.34 (4.7)	0.050	0.44 (0.1)	0.10 (0.3)	0.605
ER visit, mean (SD)	0.51 (1.4)	0.67 (1.8)	0.259	0.02 (0.2)	0.09 (0.8)	0.154
Inpatient hospital stay, mean (SD)	0.06 (0.3)	0.08 (0.3)	0.507	0.03 (0.2)	0.02 (0.2)	0.875
Length of hospital stay, days, mean (SD)	0.29 (1.9)	0.50 (3.3)	0.365	0.15 (1.6)	0.23 (2.3)	0.658
Prescriptions, mean (SD)	12.34 (9.5)	13.83 (11.0)	0.090	5.04 (3.4)	5.14 (3.7)	0.721

ER=emergency room; SD=standard deviation.

Follow-up Depressive Disorder-Related Costs

The difference in unadjusted depressive disorder-related total costs were not statistically significant by 3 months ($P=0.536$; Tables 2 and 4) or by 6 months ($P=0.387$). The largest cost drivers were inpatient care, which accounted for approximately two-thirds of the total depressive disorder-related costs, followed by outpatient hospital visits, office visits, and pharmacy costs, with each accounting for less than one-quarter of the costs. The outpatient hospital costs at 6-months post-index were significantly higher ($P=0.030$) among the cognitive dysfunction cohort compared with the cognitive normal cohort. The median costs were similar across the 2 cohorts for the 3-month and 6-month total costs and cost components.

In the adjusted gamma model, patients with cognitive dysfunction had significantly higher 3-month depressive disorder-related total costs (\$718) compared with patients without cognitive dysfunction (\$406, $P<0.001$; Table 2). The cost ratio (see Appendix F, available in online article) indicated 1.77 times (95% CI=1.30-2.41, $P<0.001$) higher depressive disorder-related costs for patients with cognitive dysfunction than those without.

In addition, baseline Quan-Charlson score >0 and full-time employment were significantly and positively associated with all-cause costs during the 3-month follow-up period. At 6 months, the ratio was 1.30 times (95% CI=0.98-1.72, $P=0.071$) higher costs for patients with cognitive dysfunction. Baseline Quan-Charlson score >0 and full-time employment

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TABLE 4 Mean (SD) and Median 3- and 6-Month Unadjusted All-Cause and Depressive Disorder-Related Health Care Costs by Cohort

		All-Cause Costs		P Value	Depressive Disorder-Related Costs		P Value
		Cognitive Normal (n = 308, \$)	Cognitive Dysfunction (n = 255, \$)		Cognitive Normal (n = 308, \$)	Cognitive Dysfunction (n = 255, \$)	
3 Months							
Total	mean (SD)	2,312 (8,266)	3,948 (14,643)	0.113	564 (4,099)	951 (9,255)	0.536
	median	669	695		99	91	
Office visit	mean (SD)	526 (1,441)	825 (4,576)	0.317	63 (142)	66 (132)	0.797
	median	276	247		0	0	
Outpatient hospital visit	mean (SD)	397 (1,212)	1,139 (4,567)	0.012	42 (320)	63 (427)	0.530
	median	0	0		0	0	
Emergency room	mean (SD)	44 (149)	73 (222)	0.078	4 (45)	6 (38)	0.516
	median	0	0		0	0	
Inpatient	mean (SD)	885 (7,677)	1,238 (11,550)	0.676	337 (4,063)	674 (9,186)	0.587
	median	0	0		0	0	
Other medical	mean (SD)	103 (484)	166 (873)	0.308	4 (50)	31 (427)	0.309
	median	0	0		0	0	
Pharmacy	mean (SD)	356 (1,122)	508 (1,151)	0.114	114 (206)	111 (215)	0.878
	median	157	163		50	40	
6 Months							
		All-Cause Costs		P Value	Depressive Disorder-Related Costs		P Value
		Cognitive Normal (n = 307, \$)	Cognitive Dysfunction (n = 252, \$)		Cognitive Normal (n = 307)	Cognitive Dysfunction (n = 252)	
Total	mean (SD)	3,938 (10,488)	6,707 (19,038)	0.040	759 (4,282)	1,316 (9,446)	0.387
	median	1,252	1,382		150	147	
Office visit	mean (SD)	860 (1,956)	1,516 (9,023)	0.259	89 (205)	96 (204)	0.674
	median	459	399		0	0	
Outpatient hospital visit	mean (SD)	920 (2,619)	2,162 (7,313)	0.011	53 (343)	209 (1,090)	0.030
	median	0	0		0	0	
Emergency room	mean (SD)	77 (212)	165 (674)	0.047	4 (46)	7 (55)	0.545
	median	0	0		0	0	
Inpatient	mean (SD)	1,217 (8,162)	1,759 (12,090)	0.544	423 (4,228)	805 (9,340)	0.548
	median	0	0		0	0	
Other medical	mean (SD)	178 (699)	262 (1,006)	0.267	5 (51)	35 (433)	0.263
	median	2	8		0	0	
Pharmacy	mean (SD)	687 (2,346)	844 (1,649)	0.353	185 (388)	164 (325)	0.471
	median	271	283		82	68	

SD = standard deviation.

were significantly and positively associated with all-cause costs during the 6-month follow-up period.

Discussion

In this study, we classified patients with depressive disorder from an ambulatory care setting into cognitive dysfunction or cognitive normal cohorts, based on standard assessments of cognitive function. We compared all-cause and depressive disorder-related costs across the 2 cohorts to determine if costs for patients with cognitive dysfunction were higher than costs for patients without cognitive dysfunction. In addition, the types of health care services that accounted for the costs for each cohort were identified. For all patients, regardless of

cognitive dysfunction, the main drivers of all-cause costs prior to and following antidepressant initiation were office visits, outpatient hospital visits, and inpatient costs. The main driver of depressive disorder-related costs was inpatient costs. These results for depressive disorder-related costs are consistent with results from a systematic review of cost-of-illness studies in depression that found inpatient costs to be cost drivers, followed by outpatient costs and pharmacy costs.⁵

The cognitive normal cohort had more patients who were white and employed full time; this cohort also had higher education and fewer comorbidities. Thus, the associations between cognitive dysfunction and total follow-up costs were tested with adjustment for potential confounders. After

adjustment, compared with patients without cognitive dysfunction, patients with cognitive dysfunction had significantly higher all-cause and depressive disorder-related health care costs over 3 months and higher all-cause costs over 6 months. Over 6 months, the difference in unadjusted all-cause costs between patients with cognitive dysfunction and those without was \$2,769 (\$6,707-\$3,938); controlling for potential confounders, the difference was \$1,110 (\$4,793-\$3,683). These differences in all-cause costs may be attributed to the greater need for follow-up services in patients with cognitive dysfunction, that is, to the additional cost of treating cognitive dysfunction following antidepressant treatment. Likewise, the difference over 6 months in unadjusted depressive disorder-related costs was \$557 (\$1,316-\$759); controlling for confounders, it was \$177 (\$771-\$594). These differences in costs could also be attributable to the additional depressive disorder-related treatment of cognitive dysfunction (greater need for follow-up services in patients with cognitive dysfunction).

We are not aware of any published work measuring the additional costs of treating cognitive dysfunction in patients with depressive disorders against which to compare our results. However, 2 studies did measure the additional costs of other concomitant conditions in patients with MDD. One study, a U.S. claims-based study, found increased costs in patients with MDD who were taking insomnia medication.²⁵ Patients taking insomnia medication had higher annual adjusted all-cause costs (\$3,918 more) and adjusted MDD-related costs (\$537 more), compared with MDD patients not taking insomnia medication. Another U.S. claims-based study found that patients with MDD and anxiety had higher annual costs (\$10,031) than patients with MDD only (\$6,681), a difference of \$3,350.²⁶ Our unadjusted all-cause cost of treating patients with cognitive dysfunction over 6 months was \$2,769, and our adjusted cost was \$1,110; annualized, these are \$5,538 and \$2,220. These numbers are comparable with the all-cause costs of insomnia at \$3,918 and anxiety at \$3,350. Our unadjusted depressive disorder-related cost of treating patients with cognitive dysfunction over 6 months was \$557, and our adjusted cost was \$177, which when annualized are \$1,114 and \$354—comparable to the MDD-related cost of insomnia at \$537.

The annual cost to treat patients with MDD only (\$6,681) in the study of MDD with anxiety,²⁶ and the unadjusted cost to treat MDD patients without insomnia (\$7,015),²⁵ can be compared with the cost of our depressive-disorder patients without cognitive dysfunction to compare the costs of treating depression. Our annualized (unadjusted all-cause \$7,876 [$3,938 \times 2$] and adjusted all-cause \$7,366 [$3,683 \times 2$]) costs were similar. The mean unadjusted annual MDD-related cost in patients without insomnia was \$824,²⁵ compared with the depressive disorder-related costs of our patients without cognitive dysfunction, when our costs are annualized (unadjusted depressive disorder-related \$1,518 [759×2] and adjusted depressive disorder-related \$1,188 [594×2]). The systematic review of

cost-of-illness studies of depression found an average annual direct medical cost of \$1,000 to \$2,500.

Another study found that patients with diabetes and a dementia diagnosis in 2005 had total average Medicare payments in 2006 of \$20,655 compared with \$12,979 in patients with diabetes and no dementia diagnosis, for a difference of \$7,676.¹¹ This cost of dementia is higher than our annualized unadjusted all-cause cost of \$5,538 and our annualized adjusted all-cause cost of \$2,220 for treating cognitive dysfunction. Our lower costs for cognitive dysfunction is not surprising because patients with dementia have more severe cognitive dysfunction, and there are other additional confounders, such as comorbidities, age, and medication. Although we did not measure the long-term consequences of not treating cognitive dysfunction, our data support the consideration that cognitive dysfunction is an important symptom with cost implications similar to other chronic illnesses.

In fact, a recent meta-analysis identified cognitive deficits in patients with first-episode MDD and suggested that cognitive deficits appear to be a feasible early marker and target for early intervention in MDD.¹⁹ Patients in our study with cognitive dysfunction had higher all-cause and depressive disorder-related costs compared with patients with no cognitive dysfunction, and this difference persisted for all-cause costs through 6 months. Therefore, identifying and treating cognitive dysfunction and depressive disorder may save downstream costs to the health care system.

Limitations

We acknowledge several limitations of this study. The original study was designed to compare clinical outcomes between groups, and the secondary objective was to compare costs.¹⁵ Direct medical costs were included in the results; however, indirect costs can be substantial and were not included.⁵ The total follow-up costs were adjusted for potential confounders; however, the component follow-up costs (and baseline costs) were not adjusted because several components of total follow-up costs had zero costs, which is not conducive to a model-based adjustment. The severity of baseline depression could not be determined and therefore was also not included as a potential confounder. This sample was drawn from a much larger sample population, and a selection bias could exist. However, this lack of representativeness does not invalidate the results of the study, since the mechanisms underlying higher health care costs for depressed patients with cognitive dysfunction can be considered as independent of the representativeness of the sample, as with most relations identified in epidemiological studies.²⁷ The sample includes only patients with commercial insurance, who were aged 18-65 years and 80% female, and most of whom were employed, so it may not be representative of the general population. The nature of claims data collection limited the speed with which identification, recruitment, and participation in the survey followed the index date

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(antidepressant initiation). Patients with cognitive dysfunction at the index date may have benefitted from treatment and been classified as cognitive normal by the time they received their telephone interviews. This may bias the results to having a higher cost in the cognitive normal group because of earlier cognitive dysfunction. The remaining patients with cognitive dysfunction may have had a higher severity of cognitive dysfunction and raised the cost in the cognitive dysfunction group. Another limitation was having cognitive dysfunction measured at 1 time point only. By 6 months, the difference between groups in depressive disorder-related costs was no longer significant after adjusting for confounders, and it could be that patients may not have remained in the original classification of cognitive normal or cognitive dysfunction. Our standard assessments were provided over the telephone. Although the interviewers were trained specifically for this study by neuropsychologists, they were not neuropsychologists themselves. In addition, our method of collectively taking results of 4 cognitive assessment measures to classify patients by cognitive function has not been validated, although each of these cognitive instruments has been validated individually.

Conclusions

In this study of patients with depressive disorder, all-cause and depressive disorder-related adjusted health care costs over 3 months were significantly higher in patients with cognitive dysfunction compared with those without cognitive dysfunction. By 6 months, although the difference in depressive disorder-related costs was no longer significant after adjusting for confounders, the adjusted all-cause costs remained significantly higher for patients with cognitive dysfunction. These data support the idea that cognitive dysfunction is associated with higher health care costs in depressed individuals and may be a useful target symptom for future treatment advances.

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Study concept and design were contributed by Walker, Samp, and Akhras, with assistance from Kurlander, Essoi, and Mahableshwarkar. Data were collected by Essoi, Walker, and Kurlander and interpreted by Patel, Yang, Mahableshwarkar, and Kurlander, with assistance from Walker. The manuscript was written primarily by Walker and Kurlander, with assistance from the other authors, and revised by Walker, Patel, and Kurlander, with assistance from the other authors.

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APPENDIX A Inclusion and Exclusion Criteria

Inclusion Criteria

At least 1 pharmacy claim for an antidepressant listed in Appendix B during the identification period based on the most currently available pharmacy claims data (approximately August and September 2012). Identification of the antidepressant will occur at the end of the month when the claims database has been updated. The *identification period* will include the current month (up to the date the database has been updated) and the prior month. The *index date* will be defined as the date of the first antidepressant pharmacy claim for the antidepressant. The antidepressant a patient receives on the index date will be defined as the *index antidepressant*.

No pharmacy claim for any antidepressant medication 6 months prior to initiation of index antidepressant; the 6-month period before the index date will be defined as the *baseline period*.

Aged 18 to 65 years as of the year of the index date.

Self-reported major depressive disorder diagnosis in the invitation reply and patient survey.

Self-reported confirmation of no diagnoses of schizophrenia, bipolar disorder, epilepsy, multiple sclerosis, Parkinson's disease, Alzheimer's disease, or Huntington's disease in the invitation reply and patient survey.

Continuous enrollment in a large commercial U.S. health plan affiliated with OptumInsight during the baseline period.

Mental health coverage with OptumHealth Behavioral Solutions (OHBS).

Willingness to sign and return the informed consent and health information release forms.

Willingness and ability to participate in a telephone interview conducted in English.

Exclusion Criteria

Expiration of health plan enrollment 6 months or less from the index date.

Any claim with a primary or secondary diagnosis code for schizophrenia, bipolar disorder, Alzheimer's disease, epilepsy disorder, Huntington's disease, Parkinson's disease, and multiple sclerosis during the 1 year prior to initiation of index antidepressant.

Any prescription for 1 of the following conditions: schizophrenia, bipolar disorder, Alzheimer's disease, epilepsy disorder, Huntington's disease, Parkinson's disease, and multiple sclerosis during the baseline period.

APPENDIX B List of Antidepressants

Drug Class	Generic Name (Brand Name)
Aminoketone (DNRI)	bupropion SR (Budeprion SR)
	bupropion XL (Budeprion XL)
	bupropion (Wellbutrin)
	bupropion SR (Wellbutrin SR)
	bupropion XL (Wellbutrin XL)
	bupropion XL (Forfivo XL)
	bupropion (Aplenzin)
	bupropion/diet suppl (Appbutamone)
SSRI	citalopram (Celexa)
	escitalopram (Lexapro)
	fluoxetine (Prozac)
	fluoxetine (Rapiflux)
	fluoxetine (Sarafem)
	fluoxetine (Selfemra)
	fluoxetine/diet suppl (Sentroxatin)
	fluoxetine/diet suppl (Gaboxetine)
	paroxetine (Paxil)
	paroxetine (Paxil CR)
	paroxetine (Pexeva)
SNRI	sertraline (Zoloft)
	desvenlafaxine (Pristiq)
	duloxetine (Cymbalta)
	venlafaxine (Effexor)
	venlafaxine (Effexor XR)
Other	mirtazapine (Remeron)
	nefazodone (Serzone)
	trazodone (Desyrel)
	vilazodone hcl (Viibryd)

CR = controlled release; DNRI = dopamine-norepinephrine reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; SR = sustained release; SSRI = selective serotonin reuptake inhibitor; suppl = supplement; XL = extended release; XR = extended release.

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APPENDIX C ICD-9-CM Diagnosis Codes for Patient Exclusion

Code	Description	Code	Description
331.0	Alzheimer's disease	295.73	Schizoaffective disorder, subchronic with acute exacerbation
331.82	Dementia with parkinsonism	295.74	Schizoaffective disorder, chronic with acute exacerbation
332.0	Paralysis agitans	295.75	Schizoaffective disorder, in remission
333.4	Huntington's chorea	295.80	Other specified types of schizophrenia, unspecified condition
340	Multiple sclerosis	295.81	Other specified types of schizophrenia, subchronic condition
295.00	Simple schizophrenia, unspecified condition	295.82	Other specified types of schizophrenia, chronic condition
295.01	Simple schizophrenia, subchronic condition	295.83	Other specified types of schizophrenia, subchronic condition with acute exacerbation
295.02	Simple schizophrenia, chronic condition	295.84	Other specified types of schizophrenia, chronic condition with acute exacerbation
295.03	Simple schizophrenia, subchronic condition with acute exacerbation	295.85	Other specified types of schizophrenia, in remission
295.04	Simple schizophrenia, chronic condition with acute exacerbation	295.90	Unspecified schizophrenia, unspecified condition
295.05	Simple schizophrenia, in remission	295.91	Unspecified schizophrenia, subchronic condition
295.10	Disorganized schizophrenia, unspecified condition	295.92	Unspecified schizophrenia, chronic condition
295.11	Disorganized schizophrenia, subchronic condition	295.93	Unspecified schizophrenia, subchronic condition with acute exacerbation
295.12	Disorganized schizophrenia, chronic condition	295.94	Unspecified schizophrenia, chronic condition with acute exacerbation
295.13	Disorganized schizophrenia, subchronic condition with acute exacerbation	295.95	Unspecified schizophrenia, in remission
295.14	Disorganized schizophrenia, chronic condition with acute exacerbation	296.7	Bipolar I disorder, most recent episode (or current) unspecified
295.15	Disorganized schizophrenia, in remission	296.00	Bipolar I disorder, single manic episode, unspecified
295.20	Catatonic schizophrenia, unspecified condition	296.01	Bipolar I disorder, single manic episode, mild
295.21	Catatonic schizophrenia, subchronic condition	296.02	Bipolar I disorder, single manic episode, moderate
295.22	Catatonic schizophrenia, chronic condition	296.03	Bipolar I disorder, single manic episode, severe, without mention of psychotic behavior
295.23	Catatonic schizophrenia, subchronic condition with acute exacerbation	296.04	Bipolar I disorder, single manic episode, severe, specified as with psychotic behavior
295.24	Catatonic schizophrenia, chronic condition with acute exacerbation	296.05	Bipolar I disorder, single manic episode, in partial or unspecified remission
295.25	Catatonic schizophrenia, in remission	296.06	Bipolar I disorder, single manic episode, in full remission
295.30	Paranoid schizophrenia, unspecified condition	296.10	Manic disorder, recurrent episode, unspecified
295.31	Paranoid schizophrenia, subchronic condition	296.11	Manic disorder, recurrent episode, mild
295.32	Paranoid schizophrenia, chronic condition	296.12	Manic disorder, recurrent episode, moderate
295.33	Paranoid schizophrenia, subchronic condition with acute exacerbation	296.13	Manic disorder, recurrent episode, severe, without mention of psychotic behavior
295.34	Paranoid schizophrenia, chronic condition with acute exacerbation	296.14	Manic disorder, recurrent episode, severe, specified as with psychotic behavior
295.35	Paranoid schizophrenia, in remission	296.15	Manic disorder, recurrent episode, in partial or unspecified remission
295.40	Schizophreniform disorder, unspecified	296.16	Manic disorder, recurrent episode, in full remission
295.41	Schizophreniform disorder, subchronic	296.40	Bipolar I disorder, most recent episode (or current) manic, unspecified
295.42	Schizophreniform disorder, chronic	296.41	Bipolar I disorder, most recent episode (or current) manic, mild
295.43	Schizophreniform disorder, subchronic with acute exacerbation	296.42	Bipolar I disorder, most recent episode (or current) manic, moderate
295.44	Schizophreniform disorder, chronic with acute exacerbation	296.43	Bipolar I disorder, most recent episode (or current) manic, severe, without mention of psychotic behavior
295.45	Schizophreniform disorder, in remission	296.44	Bipolar I disorder, most recent episode (or current) manic, severe, specified as with psychotic behavior
295.50	Latent schizophrenia, unspecified condition	296.45	Bipolar I disorder, most recent episode (or current) manic, in partial or unspecified remission
295.51	Latent schizophrenia, subchronic condition	296.46	Bipolar I disorder, most recent episode (or current) manic, in full remission
295.52	Latent schizophrenia, chronic condition	296.50	Bipolar I disorder, most recent episode (or current) depressed, unspecified
295.53	Latent schizophrenia, subchronic condition with acute exacerbation	296.51	Bipolar I disorder, most recent episode (or current) depressed, mild
295.54	Latent schizophrenia, chronic condition with acute exacerbation	296.52	Bipolar I disorder, most recent episode (or current) depressed, moderate
295.55	Latent schizophrenia, in remission		
295.60	Schizophrenic disorders, residual type, unspecified		
295.61	Schizophrenic disorders, residual type, subchronic		
295.62	Schizophrenic disorders, residual type, chronic		
295.63	Schizophrenic disorders, residual type, subchronic with acute exacerbation		
295.64	Schizophrenic disorders, residual type, chronic with acute exacerbation		
295.65	Schizophrenic disorders, residual type, in remission		
295.70	Schizoaffective disorder, unspecified		
295.71	Schizoaffective disorder, subchronic		
295.72	Schizoaffective disorder, chronic		

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APPENDIX C ICD-9-CM Diagnosis Codes for Patient Exclusion *(continued)*

Code	Description	Code	Description
296.53	Bipolar I disorder, most recent episode (or current) depressed, severe, without mention of psychotic behavior	345.3	Epileptic grand mal status
296.54	Bipolar I disorder, most recent episode (or current) depressed, severe, specified as with psychotic behavior	345.40	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, without mention of intractable epilepsy
296.55	Bipolar I disorder, most recent episode (or current) depressed, in partial or unspecified remission	345.41	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, with intractable epilepsy
296.56	Bipolar I disorder, most recent episode (or current) depressed, in full remission	345.50	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures, without mention of intractable epilepsy
296.60	Bipolar I disorder, most recent episode (or current) mixed, unspecified	345.51	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures, with intractable epilepsy
296.61	Bipolar I disorder, most recent episode (or current) mixed, mild	345.60	Infantile spasms without mention of intractable epilepsy
296.62	Bipolar I disorder, most recent episode (or current) mixed, moderate	345.61	Infantile spasms with intractable epilepsy
296.63	Bipolar I disorder, most recent episode (or current) mixed, severe, without mention of psychotic behavior	345.70	Epilepsia partialis continua without mention of intractable epilepsy
296.64	Bipolar I disorder, most recent episode (or current) mixed, severe, specified as with psychotic behavior	345.71	Epilepsia partialis continua with intractable epilepsy
296.65	Bipolar I disorder, most recent episode (or current) mixed, in partial or unspecified remission	345.80	Other forms of epilepsy and recurrent seizures, without mention of intractable epilepsy
296.66	Bipolar I disorder, most recent episode (or current) mixed, in full remission	345.81	Other forms of epilepsy and recurrent seizures, with intractable epilepsy
296.80	Bipolar disorder, unspecified	345.90	Unspecified epilepsy without mention of intractable epilepsy
296.81	Atypical manic disorder	345.91	Unspecified epilepsy with intractable epilepsy
296.89	Other and unspecified bipolar disorders	649.40	Epilepsy complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable
345.00	Generalized nonconvulsive epilepsy without mention of intractable epilepsy	649.41	Epilepsy complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition
345.01	Generalized nonconvulsive epilepsy with intractable epilepsy	649.42	Epilepsy complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication
345.10	Generalized convulsive epilepsy without mention of intractable epilepsy	649.43	Epilepsy complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
345.11	Generalized convulsive epilepsy with intractable epilepsy	649.44	Epilepsy complicating pregnancy, childbirth, or the puerperium, postpartum condition or complication
345.2	Epileptic petit mal status		

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

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APPENDIX D List of Medications for Patient Exclusion

Condition	Generic Name (Brand Name)	Condition	Generic Name (Brand Name)
Schizophrenia	amitriptyline/perphenazine (Triavil)	Bipolar disorder/ epilepsy	primidone (Mysoline)
	amitriptyline/perphenazine (Etrafon)		gabapentin (Neurontin)
	chlorpromazine (Thorazine)		ethosuximide (Zarontin)
	fluphenazine (Prolixin)		ezogabine (Potiga)
	fluphenazine (Permitil)		felbamate (Felbatol)
	haloperidol (Haldol)		lacosamide (Vimpat)
	loxapine (Loxitane)		lamotrigine (Lamictal)
	mesoridazine (Serentil)		lamotrigine (Lamictal XR)
	molindone (Moban)		levetiracetam (Keppra)
	perphenazine (Trilafon)		levetiracetam (Keppra XR)
	pimozide (Orap)		oxcarbazepine (Trileptal)
	thioridazine (Mellaril)		rufinamide (Banzel)
	thiothixene (Navane)		tiagabine (Gabitril)
	trifluoperazine (Stelazine)		vigabatrin (Sabril)
	triflupromazine (Vesprin)		zonisamide (Zonegran)
	aripiprazole (Abilify)	Alzheimer's disease	donepezil (Aricept)
	asenapine (Saphris)		tacrine (Cogenex)
	clozapine (Clozaril)		rivastigmine (Exelon)
	clozapine (Fazaclo)		galantamine (Razadyne)
	iloperidone (Fanapt)		galantamine (Razadyne ER)
	lurasidone (Latuda)		memantine (Namenda) and XR
	olanzapine (Zyprexa)		memantine (Namenda XR)
	olanzapine/fluoxetine (Symbyax)	Multiple sclerosis	interferon β -1b (Betaseron)
Bipolar disorder/ epilepsy	paliperidone (Invega)		interferon β -1a (Avonex)
	quetiapine (Seroquel)		glatiramer acetate (Copaxone)
	risperidone (Risperdal)		interferon β -1a (Rebif)
	ziprasidone (Geodon)		natalizumab (Tysabri)
	lithium (Eskalith)		interferon β -1b (Extavia)
	lithium (Lithobid)		dalfampridine (Ampyra)
	lithium (Lithotabs)		fingolimod (Gilenya)
	carbamazepine (Tegretol)	Huntington's disease	tetrabenazine (Xenazine)
	carbamazepine (Equetro)	Parkinson's disease	carbidopa/levodopa (Parcopa)
	divalproex/valproate/valproic acid (Depacon)		carbidopa/levodopa (Sinemet)
	divalproex/valproate/valproic acid (Depakene)		carbidopa/levodopa (Sinemet CR)
	divalproex/valproate/valproic acid (Depakote)		rasagiline (Azilect)
	divalproex/valproate/valproic acid (Depakote ER)		selegiline (Eldepryl)
	divalproex/valproate/valproic acid (Stavzor)		selegiline (Zelapar)
	ethotoin (Peganone)		apomorphine (Apokyn)
	fosphenytoin sodium (Cerebyx)		pramipexole (Mirapex)
	mephenytoin (Mesantoin)		pramipexole (Mirapex ER)
	mephobarbital (Mebaral)		ropinirole (Requip)
	methsuximide (Celontin)		ropinirole (Requip XL)
	phenobarbital (Solfoton)		rotigotine (Neupro)
	phenobarbital sodium (Luminal)		entacapone (Comtan)
	phensuximide (Milontin)		tolcapone (Tasmar)
	phenytoin (Dilantin)		benztropine (Cogentin)
	phenytoin sodium (Dilantin)		trihexyphenidyl (Artane)
	phenytoin sodium (Phenytek)		biperiden (Akineton)
	phenytoin sodium extended (Dilantin)		amantadine (Symmetrel)
			carbidopa/levodopa/entacapone (Stalevo)

CR=controlled release; ER=extended release; XL=extended release; XR=extended release

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APPENDIX E Other Medications Related to Depressive Disorder Included in the Cost of Depression

Drug Class	Generic Name (Brand Name)
Antipsychotics	aripiprazole (Abilify)
	olanzapine/fluoxetine (Symbyax)
	quetiapine (Seroquel, Seroquel XR)
Anxiolytics	alprazolam (Xanax)
	buspirone (Buspar)
	diazepam (Valium)
	lorazepam (Ativan)
	chlordiazepoxide (Librium)
	meprobamate (Equanil)
	clonazepam (Klonopin)
	oxazepam (Serax)
	clorazepate (Gen-xene)
Hypnotics	chloral hydrate (Somnote)
	eszopiclone (Lunesta)
	ramelteon (Rozerem)
	temazepam (Restoril)
	triazolam (Halcion)
	zaleplon (Sonata)
	zolpidem (Ambien)

XR=extended release.

APPENDIX F Analysis of All-Cause and Depressive Disorder-Related Cost Ratios by Follow-up Period

Independent Variables	All-Cause Costs						Depressive Disorder-Related Costs					
	3-Month Follow-up ^a			6-Month Follow-up ^b			3-Month Follow-up ^a			6-Month Follow-up ^b		
	Cost Ratio	95% CI	P Value	Cost Ratio	95% CI	P Value	Cost Ratio	95% CI	P Value	Cost Ratio	95% CI	P Value
Intercept	2,128.94	1,201.05-3,773.69	<0.001	2,275.25	1,393.29-3,715.48	<0.001	1,705.35	878.78-3,309.36	<0.001	894.46	503.99-1,587.43	<0.001
Patient has cognitive dysfunction	1.53	1.17-2.02	0.002	1.30	1.02-1.66	0.034	1.77	1.30-2.41	<0.001	1.30	0.98-1.72	0.071
Patient has any mental health-related AHRQ comorbidity ^c	0.83	0.63-1.10	0.196	1.00	0.79-1.27	0.980	1.11	0.80-1.54	0.542	1.17	0.89-1.54	0.268
Baseline Quan-Charlson score >0	3.76	2.51-5.63	<0.001	4.51	3.20-6.36	<0.001	3.08	1.92-4.93	<0.001	6.30	4.19-9.47	<0.001
Patient-reported education "some college" or less ^d	1.02	0.78-1.34	0.877	0.96	0.75-1.23	0.755	0.68	0.49-0.94	0.018	0.80	0.61-1.07	0.129
White race ^e	0.94	0.58-1.54	0.819	0.85	0.54-1.32	0.468	0.53	0.30-0.94	0.029	1.53	0.89-2.64	0.128
Male gender	1.15	0.83-1.60	0.399	1.28	0.95-1.71	0.100	0.42	0.30-0.61	<0.001	0.68	0.48-0.95	0.026
Age (continuous)	0.99	0.98-1.00	0.149	1.01	1.00-1.02	0.231	0.96	0.95-0.97	<0.001	0.98	0.97-0.99	0.001
Full-time employment ^f	1.40	1.06-1.85	0.017	1.00	0.78-1.28	0.987	2.02	1.47-2.78	<0.001	1.47	1.09-1.98	0.012

^aNumber of observations used: 559 out of an original population of 563.

^bNumber of observations used: 555 out of an original population of 559.

^cAgency for Healthcare Research and Quality Clinical Classification Software identification.

^dPatient's highest education level achieved (less than high school, some high school, high school or equivalent [e.g., GED], some college but no degree, 2-year degree [community or technical], college graduate, graduate school).

^ePatient's self-identification as American Indian, Alaska Native, Asian, Native Hawaiian or Pacific Islander, Black or African American, White, Other race (reporting more than 1 entry was possible).

^fPatient-reported employment status (employed full time, employed part time, homemaker, retired, unemployed, other).

AHRQ=Agency for Healthcare Research and Quality; CI=confidence interval; GED=general education development.