Depression and Diabetes: A Potentially Lethal Combination

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OBJECTIVE: To assess whether Medicare fee-for-service beneficiaries with depression and diabetes had a higher mortality rate over a 2-year period compared with beneficiaries with diabetes alone.

DESIGN: Evidence of depression was based on a physician diagnosis or self-reported prescription of an antidepressant in the year prior to screening, or a score of ≥ 3 on the Patient Health Questionnaire two-item questionnaire. Mortality was assessed bi-monthly by checking Medicare claims and eligibility files or from information from telephone contact with the participant's family. Cox proportional hazard regression models were used to calculate adjusted hazard ratios of death in depressed versus nondepressed beneficiaries with diabetes.

PARTICIPANTS: A total of 10,704 beneficiaries with diabetes enrolled in a disease management program were surveyed with a health assessment questionnaire and followed over a two-year period.

MAIN RESULTS: Comorbid depression in Medicare beneficiaries with diabetes participating in a disease management program was associated with an increased risk for all-cause mortality over a two-year period of approximately 36% to 38%, depending on the definition of depression that was used. No significant increase in rates of cause-specific mortality from macrovascular disease were found in depressed versus nondepressed beneficiaries.

CONCLUSION: Among a large Medicare cohort of fee-for-service beneficiaries with diabetes, comorbid depression was associated with an increase in all-cause mortality over a two-year period. Future research will be required to determine whether the increase in mortality associated with depression is due to potential behavioral mediators (i.e., smoking, poor adherence to diet) or physiologic abnormalities (i.e., hypothalamic-pituitary axis dysregulation) associated with depression.

KEY WORDS: depression; diabetes; mortality.

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INTRODUCTION

Depression may adversely impact outcomes of chronic illnesses, such as diabetes, in several ways.¹ Depression has been shown in patients with diabetes to be associated with poor adherence to self-care regimens, such as glucose monitoring, diet, exercise regimens and taking medications as prescribed.² Depression has been linked to having a higher number of Framingham risk factors (i.e., smoking, obesity, sedentary lifestyle) for cardiac disease in patients with diabetes.³ Depression is also associated with physiologic dysregulation of the hypothalamic-pituitary axis (HPA)⁴ and sympathetic nervous system^{5,6} as well as an increase in inflammatory markers,^{7,8} which may also adversely affect the course of diabetes. Given the adverse effect on self-care and physiologic dysregulation, it is not surprising that longitudinal studies have also shown that depression is linked with an increased risk of microvascular and macrovascular complications.⁹ Recent data has also suggested that comorbid depression is not only linked to a higher risk for diabetic complications, but also a higher risk for mortality.^{9–13}

Since 2005, five studies (from four data sets) have examined the association of depression in patients with diabetes with mortality.^{9–13} At least half of the patients with diabetes in these samples were in pre-Medicare age groups (<65 years of age). The age of the study group is important because diabetes has been shown to decrease longevity in those who develop the disease before but not after age 75.¹⁴ Four out of these recent five studies have shown that depression is associated with an increased risk of mortality in patients with diabetes.^{9–12} The total number of patients with diabetes examined in these five prior studies was approximately 6,500. In this paper, we examined the impact of comorbid depression on all cause mortality and macrovascular mortality in an older cohort of over 10,000 fee-for-service Medicare beneficiaries with diabetes enrolled in Green Ribbon Health's care management program.

METHODS

Green Ribbon Health (GRH) serves Medicare FFS beneficiaries in nine counties in the state of Florida. GRH's care management program began operation on November 1, 2005. The core of the

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GRH multi-disciplinary care coordination model is telephonic interface by a personal nurse (PN), who educates and supports participants in managing their own health and following their providers' prescribed plan of care. For complex cases that require more intensive intervention, care managers (CMs) can engage the support of a field care manager (FCM). The FCM team includes social workers and registered nurses, who interact with participants, caregivers and families in person. As a third element of GRH's program, trained community health workers (CHWs) moderate workshops to promote self management skills; CHWs also compile relevant community resources and maintain GRH's community resource directory.

All participants receive a health assessment at baseline and at least every 6–12 months, using the "Medicare Domain Assessment Tool" (MDAT) developed for GRH. Depression screening is a core requirement of GRH's program and is administered at set intervals as part of the MDAT, which includes a two-item depression screener, the Patient Health Questionnaire-2 (PHQ-2)¹⁵, and when needed a depression assessment by the PN or FCM (collectively referred to as care management). Participants screening positive for depression on the PHQ-2 are further evaluated using the PHQ-9 and can then be referred to their primary care provider or specialist for assessment, diagnosis and treatment recommendations. CMs monitor depressive symptoms and response to treatment, and provide information to participants to help them manage their symptoms and connect to appropriate resources. CMs also promote self-care and help participants communicate directly with their physician(s); for participants whose depression is not improving, CMs interface with the provider for review and adjustment of the treatment plan.

Sample

GRH's population was selected to include beneficiaries who: a) met the criteria for threshold conditions of diabetes, congestive heart failure or both based on institutional (DRG) or physician codes (ICD-9) and had a hierarchical condition category (HCC) risk score¹⁶ of 1.35 or above as indicated from the initial claims data pull, which included services provided and discharges in calendar year 2004, and b) were eligible per the eligibility database dated May 11, 2005 (pulled on May 10, 2005).

This study reports results for 10,704 of the beneficiaries assigned to GRH with diabetes or both congestive heart failure (CHF) and diabetes. We excluded beneficiaries with CHF alone, because these patients are likely to have different clinical characteristics and mortality rates compared to those with diabetes. We excluded beneficiaries who were determined by GRH to be ineligible for the program in practice, based on the eligibility criteria described above; those who declined to enroll in the program or could not be contacted during the enrollment process; those who did not complete an initial Medicare Domain Assessment Tool, which we designate as MDAT₁; or those with CHF alone.

Data and Measures

Data on GRH's beneficiaries come from three main sources: MDATs administered by GRH; data on beneficiary-reported use of prescription drugs, assessed via periodic interviews conducted by GRH's CMs (typically in conjunction with MDATs); and Medicare eligibility and claims data provided to GRH by CMS.

Demographics

Limited demographic information was available via Medicare claims, including beneficiaries' age, sex, and race/ethnicity. Other sociodemographic measures, particularly education, literacy, employment status, and occupation, were available on fewer than 5% of the analysis sample.

Clinical Variables

Based on ICD-9 codes, participants' level of medical illness severity was determined using the Charlson comorbidity index (CCI).¹⁷ Evidence of cerebrovascular accident (CVA), cardiovascular event (CVD), cardiovascular procedures (coronary artery bypass surgery, angioplasty, stent placement), and end-state renal disease (ESRD) was derived from ICD-9 and CPT procedure codes. Amputations were estimated from outpatient medical claims (ICD-9 and procedure codes) from data in the one-year period prior to beneficiary screening (MDAT) and in the one-year period after screening.

Information on depression status came from three sources: ICD-9 depression codes from Medicare claims data (296.2, 296.3, 298.0, 300.4, 309.0, 309.1, 309.28, 311) in the year prior to program enrollment; the PHQ-2 screens administered as part of the MDAT (a score of ≥ 3 out of a possible 6 has been identified as the optimal cutoff on the PHQ-2 for the diagnosis of major depression);¹⁵ and participant reports of using any antidepressant medication in the prior year based on the GRH MDAT initial interview (i.e., any medication with an FDA indication for depression). The participants identified as depressed by the ICD-9 codes were included in our main survival analysis; those with possible depression, which was defined as lack of an ICD-9 code of depression but reporting use of an antidepressant medication in the prior year or scoring a ≥ 3 on the PHQ-2, were added to the ICD-9 subgroup in a sensitivity analysis.

Mortality over the 1-year period was assessed in two ways: 1) checking Medicare claims and eligibility files twice a month; and 2) information from telephone contact with the participant's family collected by GRH for the purpose of running the program.

Statistics

The descriptive statistics (e.g., mean, standard deviation, percentage) of the baseline characteristics were provided and compared between participants with and without depression diagnoses (based on ICD-9 codes in the one-year prior to MDAT) using two-sample t-tests or chi-square tests. We also compared the prevalence of previous amputation and cerebrovascular accident/cardiovascular disease between the depressed and non-depressed groups using chi-square tests. We performed the survival analyses to compare the risk of death between participants with and without depression using Cox proportional hazards models.¹⁸ Mortality was assessed for up to two years after MDAT₁ (mean in censored participants was 656 days and mean in the those who died was 412 days). Participants entered the risk set on their MDAT₁ screening date and their time-to-event variable was defined as the difference between MDAT₁ and the date of death. Baseline characteristics (age, gender, race, and Charlson comorbidity index), prior amputation, and prior CVA/CVD were also added to the model for adjustment. All analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC).

Table 1. Comparison of Patients with ICD9 Depression Diagnosis to Patients with No Depression

Variables	Categories	Overall (N=10704)	Depression in ICD-9		p-value
			Yes (N=1657)	No (N=9047)	
Demographics					
Age	Mean(SD)	75.6 (9.2)	71.0 (12.5)	76.4 (8.2)	<0.001
Male	Yes	6024 (56.3%)	712 (43.0%)	5312 (58.7%)	<0.001
Race	White	9665 (90.3%)	1498 (90.4%)	8167 (90.3%)	0.01
	Black	699 (6.5%)	91 (5.5%)	608 (6.7%)	
	Hispanic	248 (2.3%)	54 (3.3%)	194 (2.1%)	
	Other	92 (0.9%)	14 (0.8%)	78 (0.9%)	
Charlson comorbidity index (CCI)	Mean(SD)	4.3 (2.4)	4.7 (2.6)	4.2 (2.4)	<0.001
Prior conditions					
Cerebrovascular accident (CVA)	Yes	4908 (45.9%)	812 (49.0%)	4096 (45.3%)	0.01
Cardiovascular disease (CVD)	Yes	2980 (27.8%)	480 (29.0%)	2500 (27.6%)	0.27
Amputation	Yes	119 (1.1%)	25 (1.5%)	94 (1.0%)	0.09
Cardiovascular (CVD) procedure	Yes	1329 (12.4%)	179 (10.8%)	1150 (12.7%)	0.03
Conditions after MDAT1 (2 year period)					
Death	Yes	1140 (10.7%)	200 (12.1%)	940 (10.4%)	0.04
CVA	Yes	3751 (35.0%)	573 (34.6%)	3178 (35.1%)	0.67
CVD	Yes	2135 (19.9%)	324 (19.6%)	1811 (20.0%)	0.66
Amputation	Yes	90 (0.8%)	13 (0.8%)	77 (0.9%)	0.79
CVD procedure	Yes	490 (4.6%)	71 (4.3%)	419 (4.6%)	0.54
ESRD	Yes	64 (0.6%)	9 (0.5%)	55 (0.6%)	0.75

RESULTS

As shown in Table 1, a total of 1657 (15.5%) of 10,704 participants with diabetes had an ICD-9 diagnosis of depression in the 12 months prior to screening. Participants with an ICD-9 diagnosis of depression were significantly younger, more likely to be female, less likely to be African-American, more likely to be Hispanic, and had a higher severity of medical illness based on the Charlson. Participants with depression were significantly more likely to have experienced prior to screening with MDAT₁ a previous cerebrovascular accident (CVA), but were less likely to have had a recent cardiovascular disease procedure.

A total of 12.1% of participants with comorbid depression versus 10.4% of nondepressed participants died during the approximately 2-year post-screening period ($p < .05$). No differences were seen in the percentage of depressed and nondepressed participants with evidence of CVA, cardiovascular events, ESRD, or amputation in the 2-year post-screening period. As shown in Table 2 and Fig. 1, after controlling for age, gender, race/ethnicity, Charlson score, prior CVA, CVD, or CVD procedure or amputation, participants with comorbid

depression compared to those without depression had an approximately 36% increased risk of death in the 2-years post screening ($HR = 1.36$, 95% CI 1.16, 1.59). During the 2-year post-screening period, 34.6% and 19.6% of depressed participants experienced a CVA and CVD event, respectively, versus 35.1% and 20.0% of nondepressed participants. As shown in Table 3, the risk for combined CVA and CVD events in the two-year post-screening were not significantly different between depressed and nondepressed participants ($HR = 0.96$, 95% CI 0.89, 1.04).

Table 4 describes the result of a sensitivity analysis where we expanded the depression diagnosis to not only include participants with an ICD-9 diagnosis of depression in the year prior to screening, but also to those who screened positive on the PHQ-2 component of the MDAT and those treated with ≥ 1 antidepressant prescription in the year prior to screening. In this sensitivity analysis, the expanded depression diagnosis is associated with a 38% increased risk of mortality in the subsequent two-year period ($HR = 1.38$, 95% CI 1.22, 1.57).

Table 2. Survival Analysis Comparing Risk of Death by Depression Status (ICD9 Versus No Depression)

Independent variables	Hazard Ratio	95% CI	Chi-sq statistics	P-value
Depression (ICD-9)	1.36	[1.16, 1.59]	14.73	0.001
History amputation	1.77	[1.16, 2.70]	6.91	0.009
CVD, CVA or CVD procedure	1.09	[0.96, 1.24]	1.90	0.17
Age	1.05	[1.05, 1.06]	173.35	0.001
Male	1.20	[1.07, 1.36]	8.89	0.003
African American	0.94	[0.71, 1.23]	0.21	0.64
Hispanic	0.76	[0.48, 1.21]	1.36	0.24
Other race	0.70	[0.31, 1.55]	0.79	0.37
Charlson comorbidity index	1.15	[1.13, 1.17]	167.13	0.001

Figure 1. Survival curves for mortality outcome in depressed vs. nondepressed patients with diabetes.

In a second sensitivity analysis, we compared risk of mortality in beneficiaries treated with an antidepressant in the year prior to screening compared to beneficiaries with no indication of depression (i.e., no treatment with an antidepressant medication or ICD-9 depression diagnosis and PHQ-2 negative). Being treated with one or more antidepressant medications in the year prior to screening was associated with a 24% increased risk of mortality in the subsequent 2-year period (HR=1.24, 95% CI 1.01, 1.53). No difference in combined cerebrovascular and cardiovascular events was found between those treated with antidepressants versus controls without a depression indicator in the subsequent 2-year period (HR=1.04, 95% CI 0.94, 1.15).

DISCUSSION

The data from this large, high-risk subset of Medicare beneficiaries with diabetes show that comorbid depression increased the risk for mortality over a two-year follow-up period by approximately 36% to 38%, depending on the definition of depression that was used. The mortality data are consistent with results from four of the other five studies of mixed-age patients with diabetes.⁹⁻¹³ Our data suggest that depression is a significant risk factor for mortality in older participants with diabetes, even in the near term (i.e., two-year period). The mean age in the current study was 75.6 years of age, which was approximately a decade higher than previous studies.

There were no differences found between depressed and nondepressed participants with diabetes in risk for a combined cerebrovascular or cardiovascular event in the 2 years after screening. These data differ from the study by Black and colleagues⁹, which showed in a longitudinal sample of aging Hispanic patients that comorbid depression in patients with diabetes significantly increased the risk for incident macrovascular and microvascular complications compared to patients with diabetes alone. The study by Black and colleagues differed because their respondents' mean age was significantly younger (approximately two-thirds were less than 65 years of age), there was a much longer follow-up period (7-year period) and the patients were from one ethnic/racial group.⁹ Rates of mortality from vascular disease may also be decreasing in recent years in patients with diabetes due to the more aggressive treatment of blood pressure, cholesterol and glucose levels as well as widespread use of prophylactic medications such as aspirin and beta blockers.¹⁹

Table 3. Survival Analysis Comparing Risk of CVD/CVA by Depression Status (ICD9 Versus No Depression)

Independent variables	Hazard ratio	95% CI	Chi-sq statistics	P-value
Depression	0.96	[0.89, 1.04]	0.94	0.33
History amputation	1.25	[0.98, 1.59]	3.36	0.07
CVD, CVA or CVD procedure	2.92	[2.72, 3.12]	933.27	0.000
Age	1.01	[1.00, 1.01]	17.77	0.001
Male	1.04	[0.98, 1.10]	1.81	0.18
African American	0.76	[0.67, 0.87]	17.11	0.000
Hispanic	0.87	[0.71, 1.07]	1.79	0.18
Other race	0.68	[0.48, 0.96]	4.84	0.03
Charlson comorbidity index	1.05	[1.04, 1.06]	77.82	0.001

Table 4. Survival Analysis Comparing Risk of Death by Depression Status (ICD9/MDAT1/RX Versus No Depression)

Independent variables	Hazard ratio	95% CI	Chi-sq statistics	P-value
Depression	1.38	[1.22, 1.57]	24.28	0.001
History amputation	1.61	[1.07, 2.42]	5.29	0.02
CVD, CVA or CVD procedure	1.08	[0.95, 1.21]	1.44	0.23
Age	1.05	[1.05, 1.06]	194.91	0.001
Male	1.25	[1.11, 1.40]	14.14	0.001
African American	0.90	[0.69, 1.17]	0.66	0.42
Hispanic	0.72	[0.46, 1.14]	1.94	0.16
Other race	0.74	[0.35, 1.55]	0.65	0.42
Charlson comorbidity index	1.15	[1.13, 1.18]	197.49	0.001

Several prior studies have suggested that treatment with antidepressant medications may be associated with reduced mortality (or repeat myocardial infarction) after myocardial infarction²⁰ or cerebrovascular accident²¹. Our data showed that treatment with an antidepressant was associated with 24% higher mortality risk compared to nondepressed beneficiaries, but no increased risk of a combined cerebrovascular or cardiovascular event. Treatment in naturalistic care with an antidepressant is often associated with severity and persistence of depressive symptoms and few patients receive guideline level antidepressant care.²² Therefore this increased risk of mortality associated with treatment is not surprising.

Limitations of this study include: lack of generalizability given that these participants with diabetes were from one geographic region of the United States, and were older than the populations with diabetes reported in the past mortality studies.⁹⁻¹³ The two-year follow-up period was relatively short. The study depended, in part, on physician diagnosis (ICD-9 codes) and physician treatment (use of antidepressants), which usually selects for participants with greater severity of illness. There were baseline socioeconomic variables such as education and income that we were not able to adjust for. Finally, potential mediators of depression's adverse effect on clinical outcomes such as smoking, obesity, sedentary lifestyle and taking medications as prescribed were not available.

CONCLUSION

This study adds to the emerging evidence in young and middle-aged patients with diabetes that depression is also a risk factor for mortality in older fee-for-service Medicare beneficiaries with diabetes who have high levels of diabetes complications and medical comorbidity.

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