Antidepressant Medication Use for Primary Care Patients with and without Medical Comorbidities: A National Electronic Health Record (EHR) Network Study

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Background: **Because comorbid depression can complicate medical conditions (eg, diabetes), physicians may treat depression more aggressively in patients who have these conditions. This study examined whether primary care physicians prescribe antidepressant medications more often and in higher doses for persons with medical comorbidities.**

Methods: **This secondary data analysis of electronic health record data was conducted in the Centricity Health Care User Research Network (CHURN), a national network of ambulatory practices that use a common outpatient electronic health record. Participants included 209 family medicine and general internal medicine providers in 40 primary care CHURN offices in 17 US states. Patients included adults with a new episode of depression that had been diagnosed during the period October 2006 through July 2007 (n = 1513). Prescription of antidepressant medication and doses of antidepressant medication were compared for patients with and without 6 comorbid conditions: diabetes, coronary heart disease, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, and cancer.**

Results: **20.7% of patients had at least one medical comorbidity whereas 5.8% had multiple comorbidities. Overall, 77% of depressed patients were prescribed antidepressant medication. After controlling for age and sex, patients with multiple comorbidities were less likely to be prescribed medication (adjusted odds ratio, 0.58; 95% CI, 0.35–0.96), but there was no significant difference by individual comorbidities. Patients with cerebrovascular disease were less likely to be prescribed a full dose of medication (adjusted odds ratio, 0.26; 95% CI, 0.08–0.88), but there were no differences for other comorbidities or for multiple comorbidities, and there was no difference for any comorbidities in the prescription of minimally effective doses.**

Conclusions: **Patients with new episodes of depression who present to a primary care practice are not treated more aggressively if they have medical comorbidities. In fact, patients with multiple comorbidities are treated somewhat less aggressively. (J Am Board Fam Med 2010;23:499–508.)**

Keywords: **Practice-based Research, PBRN, Electronic Medical Records, Primary Health Care, Chronic Disease**

Depression is among the most common chronic conditions seen in primary care, with nearly 17% of the adult population in the community meeting criteria for major depressive disorder (MDD) during their lifetime[1] and nearly 7% experiencing MDD during a 12-month period.[2] The prevalence of MDD is even higher among those persons who receive care in the primary care setting,[3] which is where most persons who seek care for their depression receive this care.[3,4]

Although depression is common among all populations, it is more common in persons with chronic medical conditions.[5] In particular, studies

This article was externally peer reviewed.
Submitted 31 December 2009; revised 4 May 2010; accepted 6 May 2010.
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Funding: This study was funded by Wyeth Pharmaceuticals (Collegeville, PA).

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Conflict of interest: Dr. Gill was a consultant for GE Healthcare.
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have shown the prevalence of depression to be higher for persons with diabetes mellitus,[6,7] heart disease,[8–11] stroke,[7] chronic obstructive pulmonary disease (COPD),[12] and cancer.[13–15]

Comorbid depression can exacerbate the chronic medical condition or even increase mortality in persons with these chronic medical conditions. For example, studies have shown that depression is associated with worse glycemic control[16] and higher mortality[17,18] in those with diabetes; higher morbidity[19] and mortality[20] in patients after myocardial infarction; higher rates of hospitalization among stroke patients;[21] and reduced survival among cancer patients.[22] Therefore, some authors have argued that physicians should be particularly vigilant in the diagnosis and treatment of depression in persons with chronic diseases such as cancer[23] and heart disease.[10]

However, there is little evidence that primary care physicians treat depression more aggressively in patients who have comorbid medical conditions. It could be that physicians actually treat depression less aggressively in patients who have serious comorbidities, partly because of concerns about the adverse effects of antidepressant medications.[8,24] One recent study found that depressed patients who had diabetes were more likely to be prescribed antidepressant medications than patients who did not have diabetes, but patients who had coronary heart disease (CHD) were less likely to be prescribed antidepressant medications and that there was no difference for patients who had cancer or cerebrovascular disease (CVD).[25] However, that study was limited in its applicability to primary care because many of the physicians studied were specialists who do not normally treat depression.

The purpose of this analysis was to examine antidepressant treatment for patients who experienced new episodes of depression and were diagnosed in primary care offices that are part of a national research network. It was hypothesized that these patients would be more likely to be treated with antidepressants if they had chronic comorbid medical conditions including diabetes, CHD, congestive heart failure, CVD, COPD, or cancer. Second, it was hypothesized that patients who had comorbid medical conditions would be more likely to be treated with higher doses of antidepressant medications than patients who did not have these comorbid conditions.

Methods

Study Setting and Participants

This was a retrospective cohort study from a national research network called the Centricity Health Care User Research Network (CHURN). CHURN is a network of physicians and other providers in ambulatory practices that use a particular outpatient electronic health record (EHR), Centricity Provider Office (GE Healthcare, Waukesha, WI), and that have agreed to share data and participate in quality of care studies. CHURN members share data through the Medical Quality Improvement Consortium. Each office that participates in the Medical Quality Improvement Consortium regularly uploads de-identified clinical data into a central, secure repository. These data include demographic information, medications and prescriptions, diagnoses or problems, laboratory results, and other clinical data such as blood pressure, weight, and physical examination findings. The data are then cleaned, standardized, and put into a central data repository. This data repository is used by CHURN for retrospective studies about quality of care[25–28] as well as interventional studies to improve quality of care.[29] This study included CHURN members who agreed to participate in a study to improve quality of care for depression in primary care using the Patient Health Questionnaire (PHQ) 9, as well as CHURN members who agreed to be included in a comparison group that was not using the PHQ-9—this analysis examined practice patterns before the CHRUN members' participation in that interventional study. The study was granted exempt status by the institutional review board of the principal investigator's (JMG) local institution, St. Francis Hospital in Wilmington, DE.

This study included 209 providers in 40 family medicine and general internal medicine offices in 17 US states. The characteristics of these offices and providers are shown in Table 1. The majority of providers were in family medicine practices. Almost half of the practice offices had 5 or fewer providers; only 12% of offices had ≥20 providers.

For each participating practice we identified active adult (≥18 years of age) patients who received a new diagnosis of depression during the first 9 months of the 1-year study period (17 October 2006 to 16 October 2007). "Active patient" was operationally defined as a patient who had at least

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Table 1. Provider Characteristics (n = 209)

Characteristics	n (%)
Provider type	
Physician	165 (79)
Mid-level providers	44 (21)
Specialty	
Family medicine	113 (54)
Internal medicine	83 (40)
Other specialties	13 (6)
Location	
Urban	56 (27)
Suburban	134 (64)
Rural	19 (9)
Practice Size (providers, n)	
1–5	96 (46)
6–10	48 (23)
11–20	40 (19)
>20	25 (12)

one office visit to the study provider during the study year. Individuals who were diagnosed during the final 3 months of the study year were not included because there was insufficient time to observe treatment patterns. Diagnoses were operationally defined by the presence of International Classification of Diseases (ICD) 9 codes, including major depressive disorder (ICD-9 296.2 or 296.3) or depression not otherwise specified (ICD-9 311). We did not include persons who had been diagnosed only with dysthymic disorder, mixed depression/anxiety (ICD-9 300.4), or adjustment disorder with depressed mood (ICD-9 309.0, 309.1, or 309.28) because these represent more minor forms of depression for which the benefit of medication is less certain.[30] We also excluded patients with a recorded diagnosis of mania (ICD-9 296.0), bipolar disorder (ICD-9 296.4 to 8), or schizophrenia (ICD-9 295) because it was thought that these patients would be treated differently, including a higher rate of treatment by psychiatrists. "New diagnosis" of a depressive episode was operationally defined as having no active diagnosis of depression and no prescription of any antidepressant medication during the 6 months preceding the index diagnosis. Patients who had no office visit before the index depression diagnosis were excluded because this could represent either a new episode of depression or the entry of an established diagnosis of depression for a new patient. Using this method we identified a cohort of 1513 patients who met the criteria for a new diagnosis of depression during the study period.

For each patient in this cohort we determined the presence or absence of 1 of 6 comorbid medical conditions: diabetes mellitus (ICD-9 code 250.xx); CHD (ICD-9 code 410.xx-414.xx); congestive heart failure (ICD-9 code 428.xx); CVD (ICD-9 codes 430, 431.xx-437.xx); COPD (ICD-9 codes 491.1X-491.2X, 492.XX, 494.XX, and 496.XX); or cancer (ICD-9 codes 140.xx-209.xx, except for 173.xx [nonmelanoma skin cancer]). To be considered comorbid with depression, the medical condition had to be an active diagnosis in the EHR problem list at the time of the index diagnosis of depression.

Our main outcome variable was the prescription of an antidepressant medication, as defined by the EHR medication list. We excluded tricyclic antidepressants (TCAs) and trazodone from the definition of antidepressant medications because these medications are usually used for reasons other than depression. For the remaining medications we included any medication that was prescribed at or after the diagnosis of the episode of depression up to the end of the study period. Because the study period was 1 year and we only included persons diagnosed ≥3 months before the end of the study period, the length of time each patient was observed after diagnosis ranged from 3 to 12 months.

We also examined whether or not patients had been prescribed a "minimum recommended dose" of antidepressant medication at any point during treatment. Minimum doses for each antidepressant medication were based on the lower limit of the dose range recommended by published guidelines for treatment of depression.[31] Finally, we examined whether or not patients were prescribed a "full dose" of antidepressant medication at any point during treatment; "full dose" was defined as the upper limit of the usual dose range recommended by published guidelines for treatment of depression.[31] Table 2 shows our definition of minimum and full doses for each antidepressant medication included in the outcomes. These medications were categorized by class, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, or other antidepressants (bupropion, mirtazapine and nefazodone). No patients were taking monoamine oxidase inhibitors, so these medications were not included in the table.

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Table 2. Minimum and Full Doses of Antidepressant Medication and Proportion of Patients on each Medication (n = 1163)

Medication Category	Total Patients on Medication (n [%])	Minimum Dose (mg)	Full Dose (mg)
Selective serotonin reuptake inhibitors			
Citalopram	290 (24.9)	20	40
Escitalopram	261 (22.4)	10	20
Fluoxetine	226 (19.7)	20	40
Paroxetine	66 (5.7)	20	40
Sertraline	156 (13.4)	50	100
Serotonin-norepinephrine reuptake inhibitors			
Duloxetine	72 (6.2)	30	60
Venlafaxine	78 (6.7)	75	150
Other			
Bupropion	209 (18.0)	150	300
Mirtazapine	23 (2.0)	15	30
Nefazodone	1 (0.1)	300	600

Analysis

Dichotomous variables were created for the main outcome variable (being prescribed any antidepressant medication) as well as the variables of being prescribed a minimum dose or being prescribed a full dose of medication. The 2 dose outcomes were analyzed only for persons who had been on medication for at least 3 months before the end of the study year (n = 1163) to allow time for the treating physicians to increase antidepressant medication to a stable dose. For each outcome the proportion was compared for persons who had and did not have each of the comorbid conditions as well as for who had and did not have any of the 6 conditions. Odds ratios (ORs) and 95% CIs were calculated for each comparison after controlling for age and sex using logistic regression models. We also conducted an analysis based on the number of comorbidites. We categorized persons as having none versus 1 versus ≥2 comorbitidies and compared outcomes for these 3 categories, again calculating ORs and 95% CIs for each comparison after controlling for age and sex, as described above.

Results

Table 3 shows the characteristics of the study population, including comorbidities by age and sex. Of the 1513 patients who had new episodes of depression, 20.7% had 1 of the 6 comorbid conditions;

Table 3. Characteristics of the Study Population (n = 1513)

		Age Distribution (Years)			Gender Distribution	
Comorbid Condition	Total with Comorbidity	<40 (n = 566)	40–59 (n = 601)	≥60 (n = 346)	Women (n = 967)	Men (n = 546)
Coronary heart disease	79 (5.2)	1 (1.3)	17 (21.5)	61 (77.2)	41 (51.9)	38 (48.1)
Cerebrovascular disease	46 (3.0)	0 (0.0)	6 (13.0)	40 (87.0)	29 (63.0)	17 (37.0)
Diabetes	172 (11.4)	17 (9.9)	66 (38.4)	89 (51.7)	101 (58.7)	71 (41.3)
Cancer	55 (3.6)	1 (1.8)	15 (27.3)	39 (70.9)	34 (61.8)	21 (38.2)
Congestive heart failure	21 (1.4)	0 (0.0)	2 (9.5)	19 (90.5)	13 (61.9)	8 (38.1)
Chronic obstructive pulmonary disease	51 (3.4)	0 (0.0)	14 (27.5)	37 (72.5)	30 (58.8)	21 (41.2)
Comorbidities						
0	1,200 (79.3)	548 (45.7)	498 (41.5)	154 (12.8)	783 (65.3)	417 (34.8)
1	224 (14.8)	17 (75.9)	88 (39.3)	119 (53.1)	133 (59.4)	91 (40.6)
≥2	89 (5.9)	1 (1.1)	15 (16.9)	73 (82.0)	51 (57.3)	38 (42.7)

All data shown as n (%).

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Table 4. Proportion of Patients Prescribed Any Antidepressant Medication by Comorbidity (n = 1513)

Comorbidity	Patients Who Were Prescribed an Antidepressant (%)		Likelihood of Being Prescribed Antidepressant	
	Patients with Comorbidity	Patients without Comorbidity	Odds Ratio*	95% CI
Coronary heart disease	67.1	77.4	0.72	0.43–1.20
Cerebrovascular disease	65.2	77.2	0.70	0.37–1.33
Diabetes	73.8	77.3	0.96	0.66–1.40
Cancer	63.6	77.4	0.61	0.34–1.10
Congestive heart failure	71.4	76.9	0.96	0.37–2.54
Chronic obstructive pulmonary disease	72.6	77.0	0.97	0.51–1.84
Any comorbidity	72.2	78.1	0.87	0.63–1.21

*Odds ratios for patients who have a comorbidity compared to patients who do not have a comorbidity, adjusted for age and sex.

diabetes was the most common (11.4%), followed by CHD (5.2%), cancer (3.6%), COPD (3.4%), and CVD (3.0%). Approximately 6% had ≥2 of these comorbidities. The majority of patients were aged ≥40 years (63%) and were women (64%). Comorbidities were more common among men and older persons; 82% of patients with ≥2 comorbidities were aged ≥60 years.

Overall, 1163 patients were prescribed an antidepressant medication, representing 77.4% of patients who experienced a new episode of depression. The most common class of antidepressants prescribed was the SSRI class, and citalopram was the most commonly prescribed individual medication. As shown in Table 4, the likelihood of being prescribed an antidepressant medication was not significantly different for persons who had a comorbid medical condition compared with those who did not have a comorbid medical condition, after controlling for age and sex (adjusted OR, 0.87; 95% CI, 0.63–1.21). Also, there were no significant differences according to the presence or absence of any of the individual comorbid medical conditions. However, persons who had multiple comorbid conditions were significantly less likely to be prescribed an antidepressant medication than those who had no comorbid conditions (adjusted OR, 0.58; 95% CI, 0.35–0.96).

Of those patients who received prescriptions for antidepressant medications, 91.3% were prescribed at least the minimally recommended dose of medication. Table 5 shows the likelihood of being prescribed the minimal dose of antidepressant medication by each of the comorbid conditions. After controlling for age and sex, there was no significant difference in the likelihood of being prescribed the minimally recommended dose of antidepressant medication for those who had or who did not have comorbid conditions (adjusted OR, 0.68; 95% CI, 0.40–1.14). Also, there were no significant differences according to the presence or absence of any of the individual comorbid medical conditions or for persons with multiple comorbid conditions.

Of those patients who received prescriptions for antidepressant medications, 37.7% were prescribed full doses of medication. Table 5 shows the likelihood of being prescribed full doses of antidepressant medication by each of the comorbid conditions. Patients were less likely to be prescribed a full dose of antidepressant medication if they had CVD (adjusted OR, 0.26; 95% CI, 0.08–0.88). However, there were no significant differences in the prescription of full doses of medication for persons who had any other individual comorbid medical condition, for persons who had any comorbid condition (adjusted OR, 0.88; 95% CI, 0.61–1.25), or for persons with multiple comorbid conditions (adjusted OR, 0.60; 95% CI, 0.30–1.20).

Discussion

Depression is more common among patients who have a significant medical comorbidity,[5] and its presence may increase morbidity and mortality from the comorbid condition. Depression is associated with worse glycemic control,[16] higher risk of complications,[32] and higher mortality[17] among persons who have diabetes. Depression is also associated with higher mortality among persons who have had a myocardial infarction (MI)[33] or stroke[21,34] and in patients with cancer.[13,22]

There is also some evidence that the treatment of depression improves outcomes for comorbid

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Table 5. Proportion on Minimum or Full dose Antidepressant Medication by Comorbidity (n = 1163)

Comorbidity	Minimum Dose of Antidepressant Medication				Full Dose of Antidepressant Medication			
	Patients Prescribed (%)		Likelihood of Prescription		Patients Prescribed (%)		Likelihood of Prescription	
	Patients Who Have Comorbidity	Patients Who Do No Have Comorbidity	Odds Ratio*	95% CI	Patients Who Have Comorbidity	Patients Who Do No Have Comorbidity	Odds Ratio*	95% CI
Coronary heart disease	84.9	91.6	0.83	0.36–1.88	32.1	37.9	1.07	0.58–1.98
Cerebrovascular disease	80.0	91.6	0.74	0.28–1.94	10.0	38.4	0.26	0.08–0.88
Diabetes	85.0	92.1	0.69	0.39–1.21	33.1	38.2	1.00	0.67–1.51
Cancer	82.9	91.6	0.72	0.28–1.82	31.4	37.9	1.04	0.50–2.19
Congestive heart failure	66.7	91.6	0.32	0.10–1.01	26.7	37.8	0.90	0.28–2.92
Chronic obstructive pulmonary disease	83.8	91.6	0.81	0.32–2.07	27.0	38.0	0.84	0.39–1.78
Any comorbidity	85.0	92.9	0.68	0.40–1.14	30.1	39.5	0.88	0.61–1.25

*Odds ratio for patients who have a comorbidity compared with patients who do not have a comorbidity, adjusted for age and sex.

conditions. A small study showed that treatment of depression after an MI led to fewer subsequent cardiac events.[35] A post hoc analysis of a larger, randomized trial showed a reduction in death and recurrent MI when patients were treated with antidepressant medications after an MI,[36] although the benefit was seen only for those taking SSRIs (not those taking TCAs), and the benefit was not seen in the larger, randomized trial, which included patients who had been given psychotherapy but not antidepressant medications.[37] Both SSRI and TCA antidepressants have been found to reduce mortality among patients who have had a stroke.[38] One study showed that the treatment of depression among patients who have diabetes was associated with better blood pressure control and borderline better glycemic control.[16]

Given this evidence, one might expect that primary care physicians would be more likely to prescribe antidepressant medications for depressed patients if they had significant medical comorbidities. Our results suggest that this is not the case. Primary care physicians in this study were no more likely to prescribe pharmacologic treatment to patients with medical comorbidities than to those without. They were also no more likely to prescribe higher doses of antidepressant medication for patients who had medical comorbidities. In fact, in some situations physicians were significantly less aggressive in the prescription of antidepressant medications for patients with medical comorbidites. After controlling for age and sex, patients who had multiple comorbidities were less likely to be prescribed antidepressant medications, and patients who had CVD were less likely to be prescribed full doses of these medications.

At first glance, these results may seem surprising—and disappointing. But they must be interpreted with an understanding of the uncertainty in the evidence regarding the impact of treating depression in patients with comorbidites. Although there is overwhelming evidence that depression occurs at a higher rate and is associated with greater morbidity and mortality in patients who have significant medical comorbidities, there is some controversy about whether treatment with antidepressants improves medical outcomes. For example, while one study showed improved medical outcomes when persons with diabetes were treated for their depression,[16] 2 studies showed no significant improvement in diabetes control when comorbid

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depression was treated,[39,40] and another study showed worse glycemic control with pharmacologic treatment.[41] The evidence is similarly conflicting for persons who have heart disease. Although several studies have shown improved morbidity and mortality among patients who were treated for depression after an MI,[35,36] other studies have shown no such benefit.[42] In fact, some studies have suggested that antidepressant medications may increase medical risk in some patients: one study found a higher rate of stroke and all-cause mortality among patients taking SSRIs and higher all-cause mortality among patients taking TCAs.[24] Other studies have suggested that TCAs can worsen outcomes for patients after an MI.[43] This evidence may concern primary care physicians enough so that they are cautious when prescribing antidepressant medications to patients with these comorbidities.

However, the preponderance of evidence suggests that it is not necessary to be overly cautious when prescribing for patients who have medical comorbidities. Most studies have demonstrated that SSRIs are safe and effective in persons who have both CAD[10,44] and stroke.[45–47] Even for studies that show an association of antidepressant medication with worse outcomes, authors have suggested that it may be the depression rather than the antidepressant medication that is responsible for these outcomes.[48,49] Current guidelines recommend vigilance when diagnosing and treating depression in patients who have comorbid medical conditions. For example, the American Heart Association guidelines specifically say that "whether depression affects cardiac outcomes directly or indirectly, the need to screen and treat depression is imperative."[10]

This study must be interpreted in the context of potential limitations. For example, this study shared certain limitations common to EHR-based research. First, because all data were extracted from the EHR, data that was not entered into the primary care office's EHR were not captured. This could include antidepressant medications that had been prescribed by outside providers and either not disclosed to the primary care provider or not entered by the primary care provider in the record, or the use of samples of medications that were not captured as electronic prescriptions in the record. These errors would result in an underestimation of antidepressant prescriptions. Conversely, prescribed medications could have been overestimated if they had been discontinued but not removed from the medication list. These problems are of relatively less concern in this study given its focus on new treatment episodes rather than maintenance-phase treatment. Second, we could not reliably assess the use of combined antidepressant medications (for example, low-dose bupropion plus low-dose citalopram) from prescription data. Therefore, it is likely that we underestimated the proportion of patients who were receiving more aggressive treatment because we did not include combination therapy as more aggressive treatment. Third, the analyses examined only the prescription of antidepressant medication, not pharmacy fill records or medications that were actually taken by patients. This was a reasonable limitation in a study that assessed physicians' treatment decisions. Finally, the study was limited to primary care practices that were participating in an EHR-based research collaborative, and specifically those practices that had agreed to participate in a study using the PHQ-9; therefore, the results may not be generalizable to other practice settings. However it is important to note that the study represents behavior that occurred before the PHQ-9 intervention was implemented (so the intervention could not have influenced the results), and that we also included practices that did not participate in the PHQ-9 intervention but had agreed to be included in a nonintervention comparison group. A previous observational study that included primary care and specialty physicians who were not involved in any interventional study found similar results.[25]

More importantly, this study design could not address the primary care context of competing demands[50] and patient preferences. In the presence of one or more chronic health problems, physicians and patients formally and informally set priorities for treatment and may focus on one problem while leaving others "untreated."[51–54] In this study we found a relatively high overall rate of antidepressant medication prescription (77%) in patients who had comorbid medical conditions. It is possible that this is a relative "ceiling" for medication use and that the remaining 23% represents patients for whom additional medication prescriptions are not desired or have a lower relative priority. These patients may be using multiple medications for their comorbid condition(s) and additional medications may be considered as too burdensome in

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terms of cost and potential side effects. This is supported by the fact that persons who have multiple comorbidities were significantly less likely to be prescribed medications. It is also possible that nonpharmacologic depression treatment is preferred or used at a higher rate among these patients. Psychotherapy may be seen as less burdensome to patients who are already taking multiple medications. Data about the use of psychotherapy were not available in our study. However, the evidence for psychotherapy is not necessarily better than the evidence for pharmacotherapy for patients with comorbidities. In fact, one study showed psychotherapy to be of little benefit in patients after a stroke,[55] and another study found psychotherapy to be less effective than pharmacotherapy among patients with CAD.[44]

Conclusion

This study found that primary care providers do not treat depression more aggressively in patients who have medical comorbidites, and, in fact, primary care providers sometimes treat these patients less aggressively. Although less-aggressive treatment may be appropriate in some cases, in other cases it may mean that patients are not being appropriately treated for their depression. This could not only result in unnecessary morbidity from the depression itself, but also higher morbidity from the medical condition. Future research about how the treatment of depression benefits medical comorbidities could be very helpful in guiding the treatment decisions of primary care providers, particularly qualitative studies that include exploration of treatment priorities and patient preferences.

The authors would like to thank Ms. Angela Grimes for her assistance with the preparation of data and Ms. Cheryl Mongillo for her assistance with manuscript preparation.

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