Improving Depression Care in Patients with Diabetes and Multiple Complications

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BACKGROUND: Depression is common in patients with diabetes, but it is often inadequately treated within primary care. Competing clinical demands and treatment resistance may make it especially difficult to improve depressive symptoms in patients with diabetes who have multiple complications.

OBJECTIVE: To determine whether a collaborative care intervention for depression would be as effective in patients with diabetes who had 2 or more complications as in patients with diabetes who had fewer complications.

DESIGN: The Pathways Study was a randomized control trial comparing collaborative care case management for depression and usual primary care. This secondary analysis compared outcomes in patients with 2 or more complications to patients with fewer complications.

PATIENTS: Three hundred and twenty-nine patients with diabetes and comorbid depression were recruited through primary care clinics of a large prepaid health plan.

MEASUREMENTS: Depression was assessed at baseline, 3, 6, and 12 months with the 20-item depression scale from the Hopkins Symptom Checklist. Diabetes complications were determined from automated patient records.

RESULTS: The Pathways collaborative care intervention was significantly more successful at reducing depressive symptoms than usual primary care in patients with diabetes who had 2 or more complications. Patients with fewer than 2 complications experienced similar reductions in depressive symptoms in both intervention and usual care.

CONCLUSION: Patients with depression and diabetes who have multiple complications may benefit most from collaborative care for depression. These findings suggest that with appropriate intervention depression can be successfully treated in patients with diabetes who have the highest severity of medical problems.

KEY WORDS: depression; diabetes mellitus; primary care.
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Depression is twice as common in patients with diabetes mellitus compared with other patients in primary care settings, affecting 11% to 15% of this group.[1] The prevalence of depression may be even higher in patients with diabetes who have multiple complications.[2,3] Yet depression in patients with diabetes is often inadequately treated within primary care.[4]

Depression may be an important barrier to effective diabetes management. It has been associated with poor adherence to diet, exercise and medication regimens,[5–8] as well as higher hemoglobin A_{1c} (HbA_{1c}) levels,[9] greater symptom burden, and greater functional impairment.[6,7,10] In addition, depression has been associated with the development of complications and mortality.[2,11–13]

While depression may contribute to poor diabetes-related outcomes, diabetes and its complications may also contribute to poor depression outcomes. Diabetes symptoms, such as neuropathic pain and fatigue, may result in prolonged or recurrent episodes of depression, as well as nonresponsiveness to treatment for depression. Trials conducted in primary care populations have generally found that patients with medical comorbidities are less responsive to treatment for depression,[14,15] although results have been mixed.[16,17]

In this report, we examined whether a collaborative care intervention for depression is as effective in patients with severe diabetes, defined as having 2 or more complications, as in patients with less severe diabetes, defined as having fewer than 2 complications. We have previously shown that patients with 2 or more complications had a significantly increased risk of mortality over 3 years.[13] Given that patients with 2 or more complications may have persistent depressive symptoms, we examined whether collaborative care would be particularly beneficial to this group. We hypothesized that patients with 2 or more complications would show greater benefits from the increased intensity and quality of care provided by the depression care managers than similar patients treated in usual primary care, and that these benefits would be less pronounced among patients with fewer complications. We also hypothesized that patients with 2 or more complications would receive better quality depression care from the care managers, defined as receiving 4 or more specialty mental health visits and adequate dose and duration of antidepressant medication, than similar patients in usual care.

METHODS

The Pathways Study was a randomized controlled trial that employed a collaborative care model to treat depression in 329 primary care patients with diabetes from Group Health Cooperative (GHC), a large prepaid health plan in the Pacific Northwest. The study protocol was reviewed and approved by institutional review boards at the University of Washington and GHC. All participants gave written informed consent. The intervention was previously shown to be successful at improving depressive symptoms compared with usual care.[5]

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Patients with diabetes were identified through the GHC diabetes registry. A survey was mailed to obtain demographic, psychological, and medical information, and a phone interview was conducted 2 weeks later with those patients who screened positive for depression. For inclusion, patients were required to have a Patient Health Questionnaire 9 (PHQ-9)[18,19] score of ≥ 10 on the survey and a Hopkins Symptoms Checklist (HSCL-20)[20] mean depression score > 1.1 at the telephone interview. Patients were excluded if they had communication barriers that prevented participation, planned to disenroll from GHC during the following year, were currently under the care of a psychiatrist, or had bipolar disorder or schizophrenia. Patients were not excluded for taking antidepressants as long as they had persistent symptoms. One hundred and sixty-four patients were randomized to the depression intervention and 165 to usual care.

Intervention

The intervention was an individualized stepped-care depression treatment program provided by nurse depression care managers in collaboration with primary care physicians. Treatment included an initial 1-hour appointment, followed by 2 half hour appointments (in person or by telephone) per month with the nurse care manager. In Step 1 of the intervention, patients were offered a choice of 2 evidence-based treatments: antidepressant therapy or problem-solving therapy in primary care (PST-PC). If depressive symptoms persisted ($<50\%$ reduction in severity based on PHQ-9) 8 to 12 weeks following treatment initiation, patients received Step 2 of the intervention, which included: (a) switching antidepressant medications, (b) switching to PST-PC from antidepressant medication or vice versa, (c) augmenting initial treatment with PST or antidepressant medication, or (d) obtaining consultation from study psychiatrists. If depressive symptoms persisted 8 to 12 weeks following Step 2 adjustments, or if the patient and clinician were dissatisfied with outcomes, then patients were referred to the GHC mental health system for long-term follow-up (Step 3). Once patients experienced a significant decrease in clinical symptoms ($\geq 50\%$ reduction on PHQ-9), they began a continuation phase of the intervention which consisted of monthly telephone contacts with the nurse care managers. For patients with persistent symptoms or social isolation, nurses offered monthly groups instead of phone calls.

Usual Care

Usual care patients were advised to consult with their primary care physicians about depression. At GHC, primary care physicians frequently prescribe antidepressant medication and refer to GHC Mental Health Services. Patients could also self-refer to GHC Mental Health Services.

Measures

Outcome Variables. The HSCL-20 depression scale was used to assess changes in depression over time. It is a 20-item scale with a range of 0 to 4. A reduction in HSCL-20 scores of $\geq 50\%$, on this 20-item scale (range 0 to 4), is indicative of clinically significant improvement, and a score of <0.5 is indicative of remission. The HSCL-20 has been shown to have high reliability, validity, and sensitivity to change.[20–22] It was administered by a blinded survey team at baseline, 3-, 6-, and 12-month follow-up. Hemoglobin A_{1c}, a measure of exposure of red blood cells to glucose during a 90-day period,[23] was used to assess changes in glycemic control over time. Blood draws to measure HbA_{1c} were obtained at baseline, 6, and 12 months.

Diabetes Complications. International Classification of Disease, Ninth Revision codes were used to identify 7 types of complications through GHC's automated diagnostic, pharmacy, and laboratory data: retinopathy, nephropathy, neuropathy, cerebrovascular disease, cardiovascular disease, peripheral vascular disease, and ketoacidosis. The sum of these complications is similar to a previously developed measure based on automated and clinical data that was found to correlate with medical costs in a tertiary diabetes center.[24] Mean number of complications in this sample was previously reported to be 1.5,[5] and has been shown to be associated with subsequent hospitalizations, mortality,[25] and medical costs.[26] We compared patients with fewer than 2 complications (58% of the sample) to patients with 2 or more complications (42% of the sample) because few patients had more than 3 complications and because patients with 2 or more complications had been previously shown to be at increased risk of mortality,[13] suggesting that 2 or more complications is a good proxy for disease burden. We also conducted post hoc analyses to examine number of microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular, cerebrovascular, peripheral vascular) complications separately.

Depression Process of Care. Group Health Cooperative's computerized records and study records were used to assess number of visits to mental health providers during the 12-month study. Receiving 4 or more specialty mental health visits was shown to be significantly higher in intervention compared with usual care patients.[5] Group Health Cooperative's computerized pharmacy records were used to examine antidepressant medication refills to determine whether patients received at least the minimum dosages recommended for 90 days or more within each 6-month period.[27–29] This measure of adequate dosage of antidepressants was also previously shown to be higher in intervention patients.[5]

Covariates. The mailed survey and subsequent phone interview contained questions about demographics, prior episodes of depression, comorbid anxiety, and diabetes. Computerized pharmacy records were used to obtain information about antidepressant medication use and to compute the RxRisk score,[30] a measure of chronic disease comorbidity derived from prescription drug use during the 12 months before the study. Antidepressant and hypoglycemic medications were not included in the calculation of the RxRisk score; this modified RxRisk score is considered a measure of overall medical morbidity other than depression or diabetes.

Statistical Analyses. We performed descriptive analyses to compare characteristics of patients having fewer than 2 complications with those having 2 or more, examining counts and proportions for categorical variables and computing means and standard deviations for continuous variables. Chi-square analyses with correction for continuity and 2-tailed independent group t tests were used to test for statistical significance.

Table 1. Baseline Demographic and Clinical Characteristics

	0 to 1 Complications (*N*=192)	2+ Complications (*N*=137)	χ^2 or *t*-test
Age (mean ± SD, y)	55.3 ± 11.2	62.6 ± 11.5	5.76†
Female, no. (%)	132 (68.8)	82 (59.9)	2.40
White, no. (%)	142 (75.5)	106 (82.2)	1.61
Married, no. (%)	104 (55.0)	80 (58.8)	0.32
Education (≥ 1 y of college) (%)	153 (81.0)	102 (75.6)	1.06
Working full or part time, no. (%)	112 (61.9)	43 (32.8)	24.5†
Intervention group, no. (%)	99 (51.6)	65 (47.4)	0.39
Major depression, no. (%)	124 (64.6)	92 (67.6)	0.21
Dysthymia, no. (%)	127 (66.1)	99 (72.8)	1.35
Panic disorder, no. (%)	47 (26.1)	27 (21.3)	0.71
Taking an antidepressant in year before study, no. (%)	108 (56.3)	79 (57.7)	0.02
Three or more episodes of prior depressive episodes, no. (%)	98 (51.0)	61 (44.5)	1.11
Baseline HSCL-20 score (mean ± SD)	1.6 ± 0.5	1.7 ± 0.5	0.68
Type 2 diabetes, no. (%)	189 (98.4)	126 (92.6)	5.57*
Duration of diabetes (mean ± SD, y)	6.7 ± 6.4	14.4 ± 11.1	7.89†
Age at onset of diabetes (mean ± SD, y)	48.60 ± 12.5	48.3 ± 15.2	0.21
HbA_{1c} (%), mean ± SD	7.9 ± 1.6	8.1 ± 1.5	0.80
RxRisk (mean ± SD)	2,411.6 ± 1,891.9	5,393.4 ± 4,512.2	8.20†
Retinopathy, no. (%)	8 (4.2)	69 (50.4)	92.63†
Nephropathy, no. (%)	51 (26.6)	102 (74.5)	71.79†
Neuropathy, no. (%)	26 (13.5)	85 (62.0)	81.98†
Cardiovascular disease, no. (%)	17 (8.9)	86 (62.8)	105.59†
Cerebrovascular disease, no. (%)	3 (1.6)	17 (12.4)	14.63†
Peripheral vascular disease, no. (%)	6 (3.1)	25 (18.2)	19.69†
Ketoacidosis, no. (%)	0 (0.0)	1 (0.7)	0.03

*P ≤ .05.
†P ≤ .001.
HSCL-20, the Hopkins Symptom Checklist depression scale; HbA_{1c}, hemoglobin A_{1c}; RxRisk, a measure of overall morbidity other than depression or diabetes derived from computerized pharmacy records. RxRisk scores represent annual projected health care expenses.

To explore whether the effect of the intervention varied by number of diabetes complications, we used mixed effects longitudinal regression analyses. A 3-way interaction term (treatment group by diabetes complications status by time) was used to determine whether patients with 2 or more complications showed greater improvements in clinical outcomes (continuous HSCL-20 depression scores and HbA_{1c}) from participation in the intervention over time (baseline, 3, 6, and 12 months) compared with patients having fewer complications. Models included 1 random effect (intercept) and 7 fixed effects; treatment group, complications status, time, all 2-way interaction terms, and the 3-way interaction term. Additional variables associated with complications status were subsequently added as covariates to determine if observed associations were independent of other indices of diabetes severity.

To examine whether the effect of the intervention on the quality of depression care varied by number of complications, we performed logistic regression analyses. A treatment group by diabetes complications status interaction term was used to determine whether patients with 2 or more complications experienced greater improvements in quality of depression care (≥ 4 mental health visits, adequate dosage of antidepressant medication during the first and second 6 months of the study) than patients with fewer complications. Models included treatment group, diabetes complications status, and their interaction.

RESULTS

Descriptive statistics of the sample are presented by complications status in Table 1. Mixed effect regression analyses using baseline, 3-, 6-, and 12-month follow-up of continuous HSCL-20 scores showed a greater intervention versus usual care treatment effect over time for those patients with 2 or more diabetes complications compared with those having fewer than 2 complications (treatment group by complications status by time interaction, $z = -2.26$, $P = .02$). This association remained after controlling for age, employment status, type 2 diabetes, duration of diabetes, and RxRisk ($z = -2.14$, $P = .03$). As shown in Figure 1, patients with 2 or more complications who received the Pathways collaborative care intervention experienced greater improvements in depressive symptoms than similar patients in usual primary care, while patients with fewer than 2 complications who received the intervention showed similar improvements to patients in usual care. We found a similar pattern of results using measures of depression recovery and remission (Table 2). Mixed effect regression analyses using baseline, 6-, and 12-month follow-up of continuous HbA_{1c} scores showed no effect modification for treatment group by complications status by time ($z = -0.38$, $P = .70$).

Post hoc mixed effect regression analyses using baseline, 3-, 6-, and 12-month HSCL-20 scores showed no differential effects of the intervention by number of microvascular complications ($z = -1.19$, $P = .23$). However, regression analyses showed greater intervention versus usual care treatment effects over time for those patients with more than one macrovascular complication (unadjusted treatment group by number of macrovascular complications by time interaction, $z = -2.18$, $P = .03$; adjusted, $z = -1.98$, $P = .05$).

Logistic regression analyses showed no differential effects of the intervention on quality of depression care by complications status. We observed no intervention versus usual care differences in the likelihood of receiving 4 or more mental health visits by complications status ($\chi^2 = 0.81$, $P = .37$). We

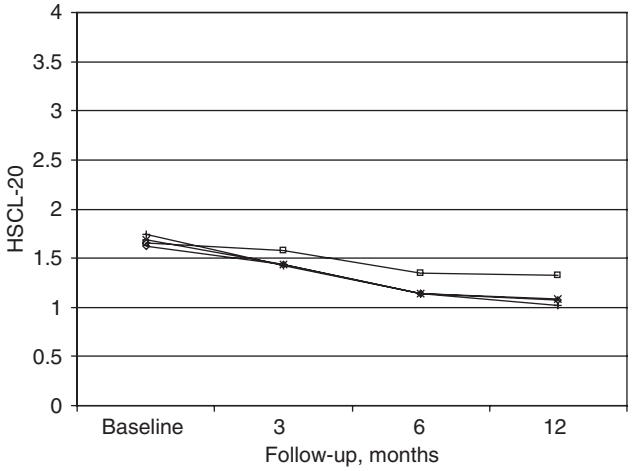

FIGURE 1. Intervention versus usual care differences by complications status on mean depression scores (range 0 to 4) from the Hopkins Symptoms Checklist depression scale. +—+, usual care with 0 to 1 complications; ×—×, usual care with 2+complications; □—□, intervention with 0 to 1 complications; ◇—◇, intervention with 2+complications. HSCL-20, Hopkins Symptom Checklist depression scale.

also observed no intervention versus usual care differences in the adequacy of antidepressant dosage by complications status (0 to 6 months, $\chi^2=2.20$, $P=.14$; 6 to 12 months, $\chi^2=0.05$, $P=.82$).

DISCUSSION

Patients with diabetes with 2 or more complications who received stepped care for depression provided by the Pathways depression care managers showed greater improvements in depressive symptomatology than patients with 2 or more complications who received usual primary care. These improvements were sustained over the full 12-month study period. Intervention and usual care patients with fewer than 2 complications showed similar improvements in depressive symptoms. A post hoc analysis showed that patients with at least 1 macrovascular complication were especially likely to benefit from the collaborative intervention compared with usual care. The results suggest that with appropriate intervention depression can be successfully treated in patients with diabetes who have even the highest severity of medical problems.

The success of the Pathways intervention over usual care in patients with 2 or more complications may be attributed to the need for additional expertise and resources when treating depression in this chronically ill population. Primary care physicians and their patients set priorities when faced with time constraints and multiple medical problems. Depression frequently "competes" unsuccessfully for attention in these circumstances.[31,32] Rost et al.[32] described that for every additional medical illness, primary care patients with depression had a decreased chance of having depression recognized and treated. The issue of competing clinical demands may be particularly relevant to the treatment of depression in patients with diabetes complications. In addition, physicians and their patients may have a difficult time determining whether symptoms are due to depression or are secondary to diabetes complications. Finally, depression, in patients with multiple medical problems, may be particularly resistant to change[14,15] and require greater management over an extended period.

While intervention patients with 2 or more complications showed greater improvements in depressive symptoms compared with usual care controls, intervention patients with fewer than 2 complications showed similar improvements to usual care. Fewer complications may have allowed patients and their physicians to focus more effectively on depression treatment within usual primary care. Also, as part of the study, patients in usual care were informed about their diagnosis of depression and encouraged to discuss it with their primary care physicians. This type of prompting was required by GHC's Human Subjects Committee and may have had a beneficial effect on outcomes in the usual care group.

Although the intervention had beneficial effects on depressive symptoms in patients with 2 or more complications, a large proportion continued to have significant depressive symptoms at 12 months. Our intervention effects are similar to other large trials,[33,34] and the results suggest a continued need for improved intervention models. Despite these difficulties, collaborative care for depression in patients with diabetes has been shown to be associated with improved clinical outcomes at no greater total ambulatory costs (due to savings in medical costs in intervention patients).[35]

Our findings contrast with 2 recent reports of similar collaborative care interventions for depression conducted in general primary care patients.[16,17] These reports suggested that while patients with greater medical comorbidities were initially more depressed than patients with fewer comorbidities, the benefits they experienced from intervention versus usual care were similar to patients with fewer comorbidities. The different findings may reflect the different samples. Our study of complications in patients with diabetes allowed us to measure the severity of medical illness with more precision than was possible in earlier studies of samples with heterogeneous medical problems. All of our patients, even those with few complications, would likely have been considered to have high comorbidities in these earlier studies.

Table 2. Depression Recovery and Remission for Usual Care Versus Intervention Groups by Complication Status

	0 to 1 Complications		2+ Complications		Fisher's Exact 1-Sided *P*	
	Usual Care	Intervention	Usual Care	Intervention	0 to 1 Complications	2+ Complications
>50% improvement on HSCL-20 at 6 months	30.5% (n=25)	35.2% (n=31)	20.9% (n=14)	39.3% (n=22)	.31	.02
<0.5 score on HSCL-20 at 6 months	20.7% (n=17)	14.8% (n=13)	7.5% (n=5)	23.2% (n=13)	.21	.01
≥50% improvement on HSCL-20 at 12 months	38.1% (n=32)	41.8% (n=38)	22.4% (n=13)	40.0% (n=22)	.37	.03
<0.5 score on HSCL-20 at 12 months	22.6% (n=19)	24.2% (n=22)	10.3% (n=6)	23.6% (n=13)	.48	.05

HSCL-20, the Hopkins Symptom Checklist depression scale.

Intervention effects on depressive symptoms were not accompanied by intervention effects on HbA_{1c},[5] and complications status did not moderate the association between treatment group and HbA_{1c}. These findings suggest that in patients with comorbid depression and diabetes, it is unlikely that treating depression in isolation will lead to improvements in diabetes control and slowed progression of the disease. Rather an integrated intervention that addresses both depression and diabetes may be needed to improve outcomes for both of these conditions.

Although the Pathways intervention led to significant improvements in quality of depression treatment compared with usual care,[5] as measured by greater than 4 mental health visits and guideline compliance with antidepressant use, the benefits did not appear to vary by complication status. Improvements in care are hypothesized to mediate the relationship between the intervention and improved outcomes. The absence of effect modification in quality of care by complications status may reflect the challenges of adequately assessing the specific processes of care which lead to improvements in depression.

Several limitations should be noted. First, this randomized trial was conducted in 1 large health care system and generalizability of the results may be limited. Second, usual care patients may have received "enhanced" usual care. These patients were encouraged to discuss depression with their primary care physicians. In addition, primary care physicians had patients in both usual care and intervention groups, and therefore usual care may have been subject to spillover effects from the intervention. Third, mean HbA_{1c} levels in these patients were low (8.0%) relative to other diabetes samples,[36] which may have limited our ability to observe improvements. Finally, the analyses presented here were post hoc and should therefore be replicated in other samples.

In sum, the collaborative stepped care intervention developed for the Pathways Study was successful at reducing depressive symptoms in patients with 2 or more diabetes complications compared with usual primary care, as well as maintaining these improvements throughout the 12-month period. Patients with fewer than 2 complications experienced marked improvement in both intervention and usual care. These findings suggest that patients with diabetes who have complex medical issues may benefit most from collaborative care for depression. This type of care is relatively inexpensive in a group known to contribute substantial costs to the health care system.[7,26] While our findings demonstrate good improvements in depression in this challenging population, we recognize that additional gains in treatment efficacy can still be made. Further research is needed to better understand how to overcome treatment barriers so that high quality depression care can be provided to patients with chronic medical problems—as this group may be most in need of mental health intervention.

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