mhc MENTAL HEALTH CLINICIAN

Original Research (Retrospective) Open Access

Post hoc depression analysis from a pharmacist-led diabetes trial

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How to cite: Bateman MT, McCarthy C, Prioli KM, Wagner ML. Post hoc depression analysis from a pharmacist-led diabetes trial. Ment Health Clin [Internet]. 2023;13(1):18-24. DOI: 10.9740/mhc.2023.02.018.

Submitted for Publication: August 12, 2022; **Accepted for Publication:** January 11, 2023

Abstract

Introduction: Diabetes and depression may present concurrently, and clinical pharmacists are well equipped to manage these conditions. Clinical pharmacists were grant funded to implement a diabetes-focused randomized controlled trial in a Federally Qualified Health Center. The objective of this analysis is to evaluate if glycemic control and depressive symptoms improve for patients with diabetes and depression with additional management from clinical pharmacists compared with those receiving the standard of care.

Methods: This is a post hoc subgroup analysis of a diabetes-focused randomized controlled trial. Pharmacists enrolled patients with type 2 diabetes mellitus (T2DM) and a glycated hemoglobin (A1C) greater than 8% and randomly assigned them to 1 of 2 cohorts, one managed by the primary care provider alone and one with additional care from the pharmacist. Pharmacists completed encounters with patients who have T2DM with or without depression to comprehensively optimize pharmacotherapy while tracking glycemic and depressive outcomes throughout the study.

Results: A1C improved from baseline to 6 months in patients with depressive symptoms who received additional care from pharmacists by −2.4 percentage points (SD, 2.41) compared with a −0.1 percentage point (SD, 1.78) reduction in the control arm (*P* .0081), and there was no change in depressive symptoms.

Discussion: Patients with T2DM and depressive symptoms experienced better diabetes outcomes with additional pharmacist management compared with a similar cohort of patients with depressive symptoms, managed independently by primary care providers. These patients with diabetes and comorbid depression received a higher level of engagement and care from the pharmacists, which led to more therapeutic interventions.

Keywords: interdisciplinary care, depressive disorder, type 2 diabetes mellitus, Federally Qualified Health Center

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Disclosures: The authors have nothing of interest to disclose

Introduction

The prevalence rate for depression is about twice as high in patients with type 2 diabetes mellitus (T2DM) compared with those without diabetes. Up to 31% of patients with diabetes have self-reported depressive symptoms.[1-3] A meta-analysis found that the prevalence was higher in low- and middle-income countries compared with high-income

countries.[4] These patients have an increased risk for hyperglycemia, decreased adherence to treatment regimens, and increased health care use.[5-7] Major depressive disorder and other depressive disorders may be recurrent in those with diabetes.[8] Therefore, the American Diabetes Association recommends that patients with diabetes be regularly assessed for depression using standardized and validated tools and be provided psychosocial care.[9]

Federally Qualified Health Centers (FQHCs) are community-based health care providers that receive funding from the Health Resources and Services Administration to provide primary care services to an underserved patient population.[10] Pharmacists have demonstrated their ability to work collaboratively with primary care providers (PCPs) to improve glycemic outcomes[11] and to provide consults for psychiatric conditions in the FQHC setting.[12] At Henry J. Austin Health Center (HJAHC), an FQHC located in Trenton, New Jersey, diabetes is the fourth most common disease state and depression is the seventh. Given the link between depression and diabetes, the complex needs of patients served by FQHCs, and that 77.4% of HJAHC's patients live at or below the poverty line, it makes sense to explore models for pharmacist collaboration in the management of comorbid diabetes and depression. This analysis evaluates whether glycemic control and depressive symptoms improve for patients with diabetes and depression with additional management from clinical pharmacists compared to those receiving the standard of care.

Methods

This is a post hoc subgroup analysis that focuses on patients who reported depressive symptoms while enrolled in a diabetes-focused randomized controlled trial (RCT). Two clinical pharmacists, a faculty member of the Ernest Mario School of Pharmacy at Rutgers University and a postgraduate year 2 pharmacy resident, were hired to lead the RCT. The pharmacists have prescriptive authority and are delegated by providers to place electronic orders. The study was approved by the Rutgers University and HJAHC Institutional Review Boards, registered with ClinicalTrials.gov (NCT03134170), and the diabetes RCT demonstrated that pharmacist comanagement of patients with diabetes can significantly improve glycemic control and patient satisfaction.[13] A detailed description of the study protocol and interventions have been published elsewhere.[13] Briefly, Medicaid-eligible adult patients with uncontrolled T2DM defined as a glycated hemoglobin (A1C) >8% were randomized in a 1:1 ratio to receive standard of care (control arm) or standard of care plus the care of a pharmacist embedded within the primary care team (intervention arm). Patients randomized to the intervention arm met with pharmacists on an as-needed basis (but at least every 3 months), generally more frequently upon enrollment into the study and less frequently over time, as determined by factors such as, but not limited to, medication regimen or severity of illness. Pharmacists met with patients for individual patient encounters, reviewed medications, set self-management goals, implemented pharmacotherapy changes, documented visits, and then completed follow-up appointments with patients on site at HJAHC. Pharmacists focused on diabetes management while also providing comprehensive medication management to address any medication therapy problems (MTPs).

A1C checks and screening questionnaires, including a depression screening with the Patient Health Quesionnaire-9 (PHQ-9), were administered at time 0 and 6 months. Patients completed the PHQ-9 assessment regardless of whether they had ever received a diagnosis of any psychiatric disorder. The PHQ-9 was used because it is the depression screening tool of choice at HJAHC. Patients were categorized as depressed if they reported experiencing $\geq$2 of the 9 symptoms from the PHQ-9, with at least 1 of the symptoms being anhedonia or feeling down, depressed, or hopeless. Symptoms must be reported on at least more than half of the days during the past 2 weeks, except suicidal ideation, which was included as a symptom if reported several days or more. The PHQ-9 data in this study were self-reported, and psychiatric disorders were not confirmed or ruled out by a formal evaluation.

The primary outcome of the post hoc depression analysis is A1C and is compared between and within depressed and nondepressed groups of patients in the control and intervention arms. The PHQ-9 score for the depressed cohort was chosen as a secondary outcome. The number of visits and time spent with the pharmacist were chosen to evaluate patient engagement. The post hoc depression analysis looks at data from time 0 to 6 months, the midpoint of the diabetes RCT. Patients that completed A1C and PHQ-9 scores at baseline and time 6 months are included in the post hoc depression analysis.

Statistical analyses were conducted for baseline data with χ^2 testing for categoric values, Kruskal-Wallis for nonparametric continuous data, and Wilcoxon rank sum testing for PHQ-9 data between the control and intervention arms. Statistical analyses were conducted to evaluate differences in changes in A1C and PHQ-9 scores at months 0 and 6. Patients were stratified by group assignment (intervention versus control) and by baseline depression status (depressed versus not depressed), yielding 4 primary comparisons of 6-month change in A1C. This stratification was conducted to analyze between and within group changes in A1C. Because of the nonnormality of the A1C data, all statistical tests for the primary comparisons were performed using nonparametric Wilcoxon rank sum tests. To combat type I error inflation due to multiple comparisons, *P* values were adjusted via the Benjamini-Hochberg procedure.[14] A1C

TABLE 1: Clinical outcomes for diabetes and depression: baseline characteristics

	Baseline (n = 132)				
	Control (n = 66)		Intervention (n = 66)		
	Not Depressed (n = 45)	Depressed (n = 21)	Not Depressed (n = 44)	Depressed (n = 22)	*P* Value
Age, mean, y	53	49	53.7	50.5	.167
Sex, male/female, n	19/26	7/14	20/24	9/13	.833
Race, n (%)					
Black or African American	29 (44)	14 (66.6)	28 (42.4)	12 (18.2)	.54
White	3 (4.5)	4 (6.1)	6 (9.1)	5 (7.6)	
Other race or not reported	13 (19.7)	3 (4.5)	10 (15.1)	5 (7.6)	
Ethnicity, n (%)					
Hispanic/Latino	12 (18.2)	4 (6.1)	10 (15.2)	7 (10.6)	.77
Not Hispanic/Latino	33 (50)	17 (25.8)	34 (51.5)	15 (22.7)	
Language, English/Spanish, n	38/7	19/2	39/5	17/5	.568
Social history, n (%)					
Alcohol use[a]	12 (18.2)	7 (10.6)	17 (25.8)	12 (18.2)	.161
High school graduate	26 (29.4)	13 (19.7)	26 (39.4)	16 (24.2)	.673
Not employed	30 (45.5)	16 (24.2)	29 (43.9)	18 (27.3)	.486
Unstable housing status	14 (21.2)	5 (7.6)	8 (12.1)	7 (10.6)	.483
No social support system	7 (10.6)	6 (9.1)	10 (15.2)	4 (6.1)	.632
Medical history					
A1C, mean, %	10.1	10.1	10	11	.07
PHQ-9 total, mean	4.8	18.5	4.5	17.6	<.001
PHQ-9 total, mean (not depressed)	4.8		4.5		.599
PHQ-9 total, mean (depressed)		18.5		17.6	.74
Self-reported mental health history, n (%)					
Any history of depression, anxiety, schizophrenia, or bipolar	13 (19.7)	15 (22.7)	14 (21.2)	12 (18.2)	.003
More than 2 of the following: depression, anxiety, schizophrenia, or bipolar	5 (7.6)	9 (13.6)	9 (13.6)	10 (15.2)	.004

A1C = glycated hemoglobin; PHQ-9 = Patient Health Quesionnaire-9.

[a]Compared no alcohol use to any frequency of alcohol use when asked, "How often does the patient report having a drink containing alcohol?"

results are expressed as percentage points (pp) to clearly indicate an absolute A1C change. A secondary analysis was performed to compare 6-month changes in PHQ-9 score between the intervention and control groups using a 2-sided independent samples *t* test. The Pearson correlation coefficient is used to indicate correlation for the patient engagement end points.

Results

Of the 238 patients enrolled in the RCT, 132 met inclusion for the post hoc depression analysis. See the demographic data in Table 1 and A1C changes in Table 2. For the control group, the A1C improved from baseline to 6 months by −0.8 pp (SD, 2.63) in patients who were not depressed and by −0.1 pp (SD, 1.78) for the depressed patients ($P = .129$). Larger 6-month A1C improvements were observed in the intervention arm, with the nondepressed cohort experiencing a −1.7 pp (SD, 2.18 pp) A1C improvement and the depressed cohort experiencing a −2.4 pp (SD, 2.41 pp) A1C improvement ($P = .3239$). Among those without depression at baseline, the improvement in A1C was −0.9 pp greater for the intervention group compared with control ($P = .0545$), whereas among those patients who did exhibit depression at baseline, the intervention group experienced an improvement of −2.3 pp above that of the control group ($P = .0081$).

A review of patient engagement during the 6-month period from baseline to midpoint shows that there was a statistically significantly higher number of visits with the pharmacist in the depressed group (5.73; SD, 3.24) compared with the nondepressed group (4.55; SD, 2.18).

TABLE 2: Between- and within-group 6-month change in glycated hemoglobin (A1C) by baseline depression status

	Difference in A1C %, mean (SD), n		
	Not Depressed	Depressed	Within-Group *P* Value[a]
Control	−0.8 (2.63), n = 45	−0.1 (1.78), n = 21	.1290
Intervention	−1.7 (2.18), n = 44	−2.4 (2.41), n = 22	.3239
Between-group *P* value[a]	.0545	.0081	

[a]The *P* values in Table 2 have been adjusted per the Benjamini-Hochberg procedure.

Similarly, the average time spent with the pharmacist was higher in the depressed group (375.65 minutes; SD, 73.67 minutes) compared with the nondepressed group (160.11 minutes; SD, 58.62 minutes). The number of visits and time with the pharmacist were both negatively correlated with the change in A1C ($r = -0.29$, $P = .017$; and $r = -0.29$, $P = .02$, respectively).

A review of MTPs by pharmacists showed a higher average number of MTPs per patient for the depressed group (11.7) compared with the nondepressed group (7.4). The number of MTPs identified was slightly negatively correlated with the change in A1C ($r = -0.11$; $P = .28$). These MTPs are categorized and reported in Table 3. Of the 22 patients with depression at baseline, the pharmacist identified MTPs related to their depression medication regimen in 6 patients. Types of interventions included addressing adverse drug effects in 5 patients (sertraline, duloxetine, bupropion, vilazodone, second-generation antipsychotic), poor adherence in 1 patient (sertraline), lack of effectiveness due to a subtherapeutic dose in 1 patient (duloxetine), and lack of treatment in 1 patient for whom the pharmacist initiated treatment with a selective serotonin reuptake inhibitor. In terms of glycemic control, Table 4 shows that pharmacists made more interventions, including adding new diabetes medications and optimizing doses, in the depressed cohort compared with the nondepressed cohort. A larger proportion of pharmacists' interventions in the nondepressed group were related to preventative care measures (eg, recommendations for vaccinations and antiplatelet therapy to address elevated risk for cardiovascular disease; 84 of 327 MTPs [25.7%]) compared with the depressed group (54 of 258 MTPs [20.9%]). More patients in the depressed group (18 of 22 patients [81.8%]) required an intervention to address adherence to diabetes therapy compared with those in the nondepressed group (25 of 44 patients [56.8%]).

Among those with baseline depression, PHQ-9 scores improved by 5.68 points in the control arm compared with 6.11 points in the intervention arm ($P = .8269$) from baseline to midpoint (Table 5).

Discussion

This paper includes data from the first 6 months of the diabetes RCT, because 6 months is sufficient timing to see improvements in A1C.[15] Between-group analysis showed greater, statistically significant, improvements in the mean A1C change for those with depressive symptoms who received additional care from the pharmacist, compared with a depressed cohort managed independently by the PCP (Figure).

Although the pharmacists did make some interventions regarding depression, it is unlikely that the larger A1C improvement in the pharmacist-managed depressive cohort is a result of improved depressive symptoms. Despite the lack of statistically significant PHQ-9 changes, pharmacists were able to provide a higher level of care to a cohort of patients with depressive symptoms, which resulted in more time with the pharmacist and more diabetes-centered interventions by the pharmacist. Because patients in the depressed group had a higher average number of MTPs per person than those in the nondepressed group, the pharmacists may have been able to implement more

TABLE 3: Summary of medication therapy problems (MTPs)[a]

	No. of MTPs		Medication-Related Need Associated With MTP			
Depression At Baseline	Total No. of MTPs	Average No. of MTPs Per Patient	Indication, n (%)	Effectiveness, n (%)	Safety, n (%)	Adherence, n (%)
Depressed (n = 22)	258	11.7	82 (31.8)	70 (27.1)	48 (18.6)	58 (22.5)
Not depressed (n = 44)	327	7.4	97 (29.7)	123 (37.6)	35 (10.7)	72 (22)

[a]MTPs are categorized per the Pharmacy Quality Alliance's MTP Categories Framework to characterize the content of pharmacists' work.

TABLE 4: Interventions to intensify diabetes regimen

Intervention	Depressed (n = 22), n (%)	Not Depressed (n = 44), n (%)
Any intervention	21 (95.5)	30 (68.2)
Initiate new diabetes medication[a]	12 (54.5)	16 (36.4)
Add new diabetes medication to current regimen	10 (45.5)	9 (20.5)
Switch diabetes medication to more effective agent	2 (9.1)	11 (25)
Initiate insulin[b]	3 (13.6)	5 (11.4)
Initiate GLP1RA[b]	2 (9.1)	4 (9.1)
Increase dose of any diabetes medication	17 (77.3)	25 (56.8)
Increased dose of insulin	13 (59.1)	22 (50)
Increased Dose of GLP1RA	1 (4.5)	0

GLP1RA = Glucagon-Like Peptide-1 Receptor Agonists.

[a]Includes any interventions to add a new diabetes medication to an existing regimen or switch a diabetes medication to a more effective agent.

[b]Applicable only to those patients who are new to the drug class.

interventions to address effectiveness of the diabetes medications in this population because of the volume of interventions recommended. Our results suggest that the improvement in A1C is more likely related to higher levels of engagement and more targeted interventions to address adherence to and efficacy of medications for diabetes in this population with comorbid diabetes and depressive symptoms.

Because this post hoc depression analysis was conducted based on a population of patients enrolled in a diabetes RCT, there was a limited sample of patients included in the post hoc subgroup analysis. Patients in FQHCs are often transient and have multiple financial barriers, making retention for research studies difficult. Another limitation is that the depressed cohort was categorized based on patient-reported PHQ-9 scores rather than based on a formal diagnosis of depression. Additionally, behavioral health consultants were available to work with patients in the control and intervention arms, but it is possible that 1 group might have received more care from a Behavioral Health Consultant compared with the other group.

Data from this project show that those with comorbid medical and behavioral conditions, such as T2DM and depressive symptoms, experience challenges when trying to achieve optimal outcomes and that those with multiple comorbidities benefited from additional care from a pharmacist. This analysis shows improvements in A1C without change in PHQ-9 scores during 6 months, which is similar to results observed in 2 trials, one with on-site visits[16] and the other performed through telemedicine encounters,[17] conducted in a population of veterans with diabetes and depression. Results of this project helped to shape pharmacists' long-term role of managing patients with chronic, complex medical and/or behavioral conditions in coordination with PCPs of this FQHC.

TABLE 5: Participants' mean change in Patient Health Quesionnaire-9 (PHQ-9)

	Change in PHQ-9 Score, mean (n)		
	Control	Intervention	*P* Value
6 mo vs baseline	−5.68 (19)	−6.11 (19)	.4135

Conclusion

Patients with uncontrolled T2DM and depressive symptoms assigned to receive medication therapy management with the pharmacist had better diabetes outcomes than the control group. These patients with diabetes and comorbid depression received a higher level of engagement and care from the pharmacists, which led to more therapeutic interventions. Pharmacists trying to create a role for themselves in a new setting may consider targeting patients with comorbid diabetes and depression. Positive outcomes may help to justify practice site and/or university-based salary support, because this study resulted in 2 permanent full-time faculty positions that are equally funded by the FQHC and the Rutgers, Ernest Mario School of Pharmacy.

Acknowledgments

This study was funded by the Nicholson Foundation, BD (Becton, Dickinson and Company) Helping Build Healthy Communities, Direct Relief, the National Association of Community Health Centers, the Institute for Medication Access and Compliance, the Henry J. Austin Health Center, and the Rutgers Ernest Mario School of Pharmacy. *write*result LLC provided tablets, online data collection forms, data storage, and technical support without charge. Kim McGuigan, PhD, supported project development. Kemi Alli, MD, helped with obtaining funding, study design, and oversight of the clinic activities. Sarah Gregg

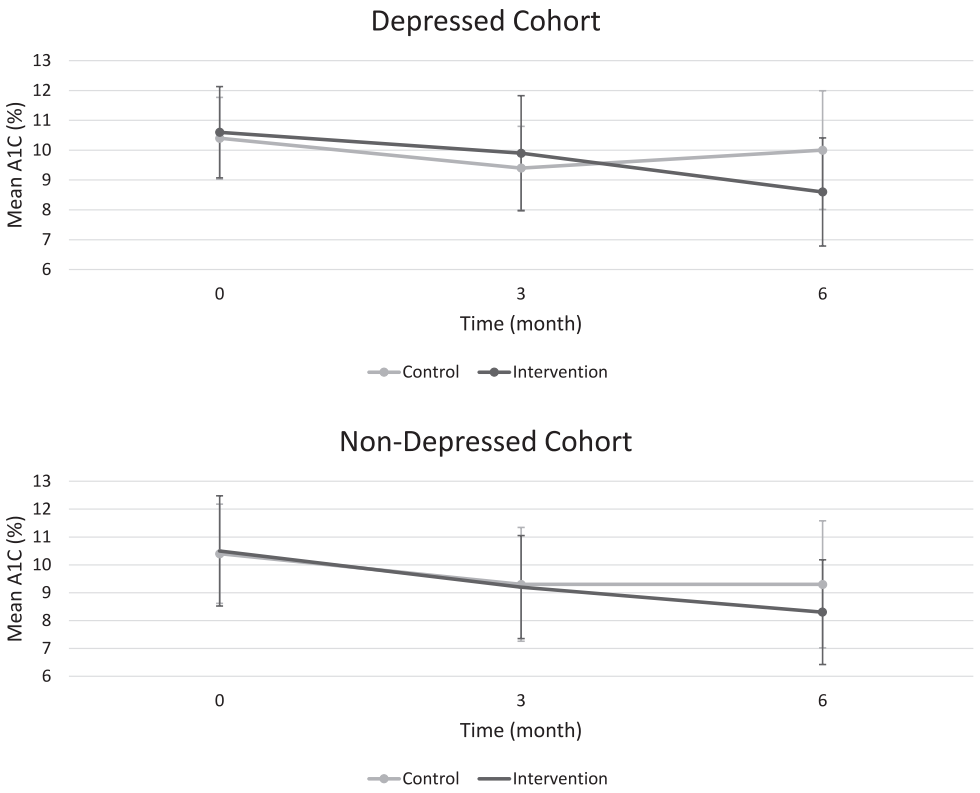

FIGURE: Mean glycated hemoglobin (A1C) by group, time point, and baseline depression status

assisted with study design and quality assurance. Drew Madsen provided quality assurance and improvement assessment. Shilonda Clemens assisted with recruiting and scheduling patients and data collection.

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