mhc
MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Correlation of antidepressant target dose optimization and achievement of glycemic control

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How to cite: Grisham-Takac C, Lai P, Srinivasa M, Vasquez L, Rascati KL. Correlation of antidepressant target dose optimization and achievement of glycemic control. Ment Health Clin [Internet]. 2019;9(1):12-7. DOI: 10.9740/mhc.2019.01.012.

Abstract

Introduction: Depression is a recognized cause of disability globally with a propensity to be comorbid in patients with diabetes, leading to poorer health-related outcomes. Although a number of studies have investigated the correlation between improvement in depression and chronic disease, none have reported on achievement of target doses of antidepressant therapies and diabetes control. The objective of this study is to determine the influence of antidepressant dosing optimization on reducing hemoglobin A1c (HbA1c).

Methods: This was a retrospective cohort study of patients seen at CommUnityCare Health Centers who were initiated on an antidepressant and had uncontrolled diabetes (HbA1c > 7%). Eligible patients were followed for 12 months after initiation and separated into those who achieved target dose and those who did not. Patient health questionnaire scores were collected when available in an attempt to quantify change in depressive symptoms.

Results: A total of 178 patients met inclusion criteria with 76 achieving an optimal dose (target group) and 102 patients below optimal dose (control group) at the end of the study period. Patients in both groups were similar at baseline with an HbA1c of 9.29% compared to 9.24% in the target and control groups, respectively. At the end of the study period, more patients in the target group achieved an HbA1c < 7% (22.9%, n = 48 vs 4.3%, n = 23, respectively; $P < .05$).

Discussion: These results suggest that optimization of antidepressant dosing in patients with diabetes may lead to an increased likelihood of reaching goal HbA1c < 7% although correlation to improvement of depression remains unknown.

Keywords: diabetes, depression, dose optimization, antidepressant

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Disclosures: P.L. was a clinical pharmacist with CommUnityCare during the development, data-analysis, and manuscript production for this research. His contributions to this publication are his own and were not performed on behalf of his current employer (Otsuka Pharmaceuticals). P.L. and the remaining authors have no other conflicts of interest to disclose.

Background

The prevalence of comorbid diabetes and depression is well documented with 9.3% of all patients with diabetes also having depression and reporting a lower quality of

life.[1] These patients have been shown to be at increased risk for poor glycemic control, lower levels of self-care, and higher medical costs.[2,3] As a result of these findings, the American Diabetes Association[4] recommends considering screening and addressing depression at least annually in all patients with diabetes. Sorkin et al[5] reported that patients with a greater severity of depression reported greater somatic symptoms of diabetes than those with lower levels of depression as defined by scores on the Center for Epidemiological Studies Depression Scale. Due to increased patient reports of hypoglycemia symptoms, diabetes treatments were less intensive and glycemic outcomes suboptimal.[5]

Several authors have reported improvement in glycemic control when clinicians address depression.[6,7] Echeverry et al[7] conducted a placebo-controlled, double-blind study following initiation of sertraline and its effect on hemoglobin A1c (HbA1c) in a low-income population. Although differences in depression scale scores were not significantly different, the study group[7] had a significantly lower HbA1c than the placebo group at 6 months (8.0% vs 8.8%, $P < .01$, respectively).

Regarding the treatment approach for pharmacologic management of major depression, the American Psychiatric Association[8] recommends that optimal treatment with antidepressants includes initiating agents at a low dose and titrating up to a target dose to improve tolerability. It has been demonstrated that titrating an antidepressant dose improves outcomes although the effective dose is not necessarily uniform between individuals. Once a patient has achieved treatment remission, the American Psychiatric Association recommends continuing these patients on an optimal dose to maintain control of symptoms. It is also recommended that a patient assessment scale, such as the patient health questionnaire (PHQ-9) be utilized to track progress.[8,9] In current literature, there is little information available regarding the achievement of optimal antidepressant dosing and its effect on glycemic control in those with comorbid diabetes and depression.

The objective of this study is to determine the effect of antidepressant target dose optimization on glycemic control.

Methods

Study Design

This was a retrospective cohort study of patients seen at CommUnityCare Health Centers with comorbid diabetes and depression who were initiated on first-line antidepressants commonly prescribed by CommUnityCare primary care providers, including selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and bupropion, between January 1, 2015, and September 30, 2015. Twelve months after antidepressant initiation, patients were separated into 2 groups: those who met target dose and those who did not. Target doses of these agents are defined in Table 1. In medications with a range, the lowest dose was used to define the target. Although the resource used was not the most up-to-date version of target or usual doses, many doses were similarly defined within the 2010 American Psychiatric Association depression guidelines.[8]

CommUnityCare is a federally qualified health center comprised of 19 locations throughout Travis County in Central Texas. Fifty-four percent of patients are uninsured, 8% are privately insured, and the remainder have Medicare or Medicaid. Electronic health records were collected from each of these centers to identify eligible patients. Such data included the start date of the antidepressant, HbA1c values, number of provider appointments kept, and number of no shows. Prior to data collection, methods were approved through the investigational review boards for CommUnityCare and the University of Texas at Austin College of Pharmacy. No external or internal funds were provided to support this research.

Subject Selection

Adults aged 18-89 years old who were initiated on an antidepressant during the study period and had uncontrolled diabetes as defined by an HbA1c $> 7\%$ within the previous 4 months were included. Additionally, patients must have kept at least 2 office visits during the study period. In an effort to exclude patients with psychiatric conditions other than major depressive disorder or treatment-resistant depression, patients with an active prescription for an antipsychotic or lithium were excluded. Other mood stabilizers, such as carbamazepine and valproic acid, were not excluded as they may also be used to treat seizure disorders.

Outcomes

The primary outcome studied was the percentage of patients achieving the American Diabetes Association's[4] general goal HbA1c $< 7\%$. Secondary outcomes included the percentage of patients reaching the less stringent goal HbA1c $< 8\%$ to account for those patients whose treatment goal may be higher, such as those with cardiovascular disease, advanced age, or hypoglycemic unawareness.[4] Change in HbA1c between groups was also investigated. Additionally, the relationship between HbA1c and PHQ-9 improvement was investigated in an attempt to discover if patients with an HbA1c $< 7\%$ were more likely to have lower PHQ-9 scores. Descriptive

TABLE 1: Initial and target antidepressant doses[14] of the study

Antidepressant	Initial, mg	Target, mg
Bupropion	300	300-450
Citalopram	20	40
Desvenlafaxine	50	100
Duloxetine	60	60-120
Escitalopram	10	20
Fluoxetine	20	40
Paroxetine	20	40
Sertraline	25	100
Venlafaxine	75	225

measures investigated were percentage of patients achieving target doses, number of encounters following antidepressant initiation, and percentage of patients prescribed insulin. Adjustments to diabetic regimen were not accounted for.

Statistical Analysis

Percentage of patients to achieve HbA1c goals was analyzed using a chi-squared test or the Fisher exact test when a cell size was less than 5 while other secondary outcomes were analyzed by a 2-sided *t* test. Differences in baseline characteristics were analyzed using ANOVA.

Results

Baseline Characteristics

During the study period, 723 patients were initiated on a low dose of an antidepressant. Of these patients, 42 patients were excluded due to an active prescription for an antipsychotic or lithium, and 184 patients were excluded due to inadequate follow-up. In addition, a total of 319 patients were excluded due to lack of baseline HbA1c or controlled HbA1c $<$ 7%. One hundred seventy-eight patients fit inclusion criteria with 76 achieving an optimal dose (target group) and 102 patients below optimal dose (control group) at the end of the study period (Figure).

Both groups were similar at baseline with patients being an average age of 52.7 years old in the target group and 53.8 years old in the control group. Patients were predominantly female (77.6% vs 79.2%), white (65.8% vs 56.9%), and uninsured (42% vs 50%) in the target and control groups, respectively. A large percentage of these patients were insulin users, with 42% in the treatment group and 40.2% in the control group. The baseline HbA1c was well above goal with an average HbA1c of 9.29% versus 9.24% in the treatment and control group, respectively (see Table 2).

Outcomes

By the end of the study period, the sample size was reduced due to lack of follow-up HbA1c values. In the target group, 48 patients had all required data (37% attrition) while only 23 patients in the control group had follow-up values (77% attrition). Of those in the target group, 22.9% met an HbA1c goal $<$7% while only 4.3% met goal in the control group ($P < .05$). This trend continued for those achieving an HbA1c $<$ 8% with 37.5% in the target group and 21.7% in the control group although the difference was not statistically significant (see Table 3).

At the end of the study period, the average HbA1c was 8.40% in the target group compared to the control

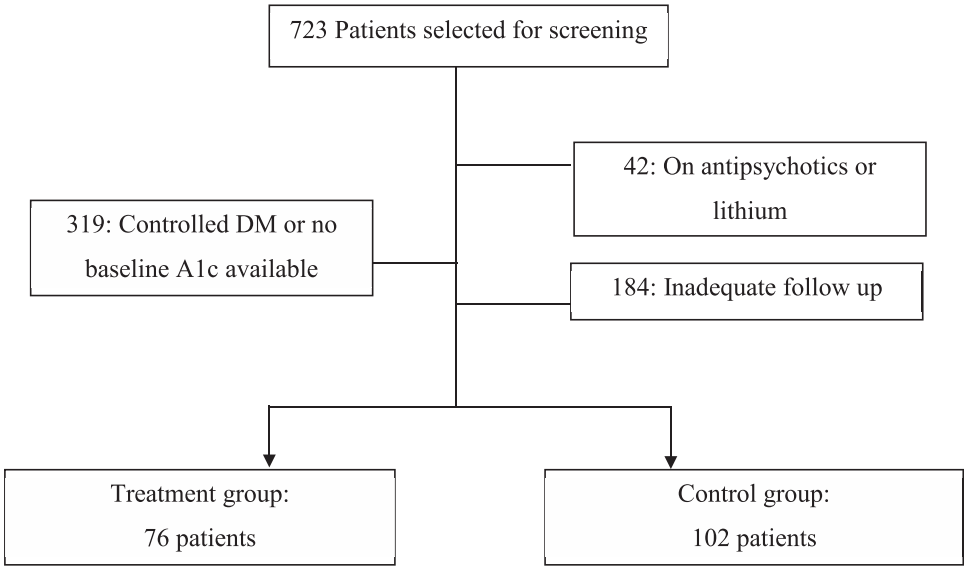

FIGURE: Description of study population selection (DM = diabetes mellitus)

TABLE 2: Baseline characteristics of the study population

Characteristic	Target (n = 76)	Control (n = 102)
Age, mean y ± SD	52.7 ± 11.2	53.8 ± 12.2
Female sex, n (%)	59 (77.6)	81 (79.2)
Race, n (%)		
Asian	2 (2.6)	5 (4.9)
African American	7 (9.2)	10 (9.8)
Unknown	17 (22.4)	29 (28.4)
White	50 (65.8)	58 (56.9)
Payer type, n (%)		
Commercial	4 (5.2)	7 (6.9)
Uninsured	32 (42)	51 (50)
Medicaid	11 (14.5)	14 (13.7)
Medicare	18 (23.7)	15 (14.7)
Unknown	11 (14.5)	15 (14.7)
Medication use, n (%)		
Insulin users	32 (42)	41 (40.2)
Oral diabetes mellitus medications, n (%)		
0	37 (48.7)	36 (35.2)
1	24 (18.4)	37(36.3)
2	12 (15.8)	27 (26.5)
3	3 (3.9)	2 (2)
Baseline hemoglobin A1c, mean % ± SD	9.29 ± 1.94	9.24 ± 1.93

group's 8.96% and not statistically different. The difference in average change in HbA1c between groups was not statistically significant (–0.55% ± 1.85 vs –0.29% ± 1.72 in the target and control groups, respectively). No differences were observed in the number of kept or no-show visits in either group. No relationship between HbA1c and PHQ-9 could be ascertained due to inadequate PHQ-9 reporting.

Discussion

Our study found that patients with uncontrolled diabetes and depression who were newly initiated on an antidepressant and subsequently titrated to the target dose were more likely to achieve a goal HbA1c less than 7% within a 12-month time period. Our results are consistent with a number of other studies,[7,10,11] thus providing further justification for titrating medication doses. A statistically significant difference did not persist for those who met HbA1c goal <8%, the reason for which was unclear. As in the aforementioned study by Echeverry et al,[7] the group initiated on sertraline had a lower HbA1c on average at the end of the trial period although the difference was not as pronounced in this study. Due to the low yield of PHQ-9 monitoring across the study population in the present study, it is difficult to ascertain the true effect of antidepressant titration on depression status. Although this is a vital piece of information to provide a full clinical picture, other data points provide support for the success of dose optimization.

There was no significant difference in the number of appointments kept between groups, meaning that patients in the target group were able to achieve goals in the same number of visits and may have been more engaged during their visits and in self-care behaviors. Additionally, it should be noted that the control group experienced a higher rate of attrition throughout the study, which could have been a function of lack of treatment optimization or another confounding factor. The analysis presented was based on a per-protocol approach as patients who had a follow-up HbA1c within 3 months of study end or treatment optimization were included in the final analysis. In an indigent patient population, this is an important realization as many of these patients have difficulty with access to care and resources. This is likely one of the reasons such a large rate of subject attrition was seen from the beginning of the study period to the end.

Limitations

A major limitation of this study was the lack of follow-up data available and resulting attrition in the study population. As a result of the small sample size, there is a limitation to the dependability and statistical signifi-

TABLE 3: Final study outcomes[a]

Outcome measured	Target (n = 48)	Control (n = 23)	*P* Value
Met goal HbA1c < 7%, n (%)	11 (22.9)	1 (4.3)	<.05
Met goal HbA1c < 8%, n (%)	18 (37.5)	5 (21.7)	.24
HbA1c	8.40 ± 1.53	8.96 ± 1.78	NS
Change in HbA1c, mean % ± SD	–0.55 ± 1.85	–0.29 ± 1.72	NS
No. of appointments kept	6.1 ± 1.69	5.65 ± 4.0	NS
No. of no-show appointments	1.44 ± 1.69	1.35 ± 1.43	NS

HbA1c = hemoglobin A1c; NS = not significant.

[a]Data representative of mean ± SD unless otherwise specified.

cance of the results. Additionally, as with any retrospective study, information collected is dependent upon what was reported in the patient chart. If laboratory values or PHQ-9 scores were documented elsewhere, this information was not made available in the data collection. Patients may also have previously been on another antidepressant while in CommUnityCare's care or have documented success with the same antidepressant from another provider, so these were not necessarily treatment-naïve patients. Furthermore, adherence to therapy was not able to be collected or assessed with assumptions that the patient was taking the optimal dose based on the presence of an active prescription. A number of factors play a role in improvement in both depression and diabetes outcomes. Although the data collected demonstrates that these patients were seen approximately the same number of times between groups, the provider type (eg, behavioral health counselor, primary care physician, clinical pharmacist, or psychiatrist) is unknown and could play a vital role in improvement of either disease state. There was also no method employed to control for diabetic-regimen changes or presence of other chronic conditions, both of which serve as potential contributors in success of achieving glycemic goals.

Scores from PHQ-9 were unavailable in 73% of patients at antidepressant initiation and in 90% of patients at follow-up. As the PHQ-9 is a well-documented tool to track depression response, lack of this data limited our ability to reliably relate dose optimization, HbA1c improvements, and depression response.

Future Directions

The most effective approach to jointly improving diabetes- and depression-related outcomes remains to be seen, but there are a number of recent studies investigating various clinical practice models in a wide variety of patient populations. The TEAMcare trial[10] utilized frequent follow up by nurse care managers for patient follow-up, goal-setting, and medication titration, resulting in increased patient satisfaction, self-care involvement, and medication titration. Most recently, the COMPASS trial[11] used a similar approach with patients who had failed usual care, finding that 40% of these patients had depression remission or treatment response and 23% achieved an A1c less than 8%. Overall, those utilizing an interdisciplinary team approach with frequent follow-up coupled with dose titration have proven to be the most successful.

The largest effect sizes have come from those practicing in a multidisciplinary environment, which results in improved patient outcomes and cost savings for the health care system. In the COINCIDE study,[12] patients with multiple comorbidities were targeted, and a collaborative approach was taken to improve self-care as well as to target medication-related issues. A modest reduction in PHQ-9 score was seen (–1.2 difference, $P = .04$). In the IMPACT trial,[13] 2 trained clinical pharmacist case managers were used to follow patients, assess their mental health, recommend medication changes, and provide nonpharmacologic strategies. Enrolled patients had a 6.2-point reduction in their PHQ-9 score ($P < .0001$). Paired improvements in diabetes-related outcomes with depression markers are only beginning to be elucidated. Further trials are needed to find the best approach for this patient population.

In the present study, the increased percentage of patients achieving HbA1c goal <7% as well as a higher chance of achieving the common performance measure of HbA1c < 8% supports the need to address depression along with patients' antiglycemic therapies. Utilizing all of the members of the health care team in addition to titration of an antidepressant to a therapeutic dose will likely improve both diabetes- and depression-related outcomes. Although this finding is independent of changes in PHQ-9 scores, increased use of this tool will play a vital role moving forward to further support changes in therapy.

Conclusion

In a patient population with uncontrolled diabetes who were initiated on antidepressants, those who were titrated to target doses on their antidepressant had a higher chance of achieving HbA1c goal <7% than those who were not optimized to a target dose. These results suggest that optimization of antidepressant dosing may lead to an increased likelihood of reaching HbA1c goal <7% although correlation to improvement of depression remains unknown.

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