WEST AFRICAN JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Effect of an Antidepressant on Medication Adherence among Type 2 Diabetic Patients with Depression Accessing Care in GOPC of FETHI

Effet de l'Antidépresseur sur l'Observance Thérapeutique chez les Patients Diabétiques de Type 2 Souffrant de Dépression et Ayant Accès aux Soins dans le GOPC de FETHI

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ABSTRACT

Comorbid depression among diabetes mellitus (DM) patients is on the increase. This has been linked with poor glycaemic control, greater risk of complications, high burden of medical cost and health care utilisation, and worsening prevalence of other comorbidities resulting in decreased life expectancy. This study determined the antidepressant effect of amitriptyline on depression and glycaemic control among the depressed type 2 DM patients attending Federal Teaching Hospital, Ido-Ekiti (FETHI), Nigeria. It was an interventional study involving 51 depressed type 2 DM patients randomly screened using Patient Health Questionnaire-9 (PHQ-9). They had health education and oral amitriptyline 50mg at night for two months. Post-intervention assessment was done using the same tool. Respondents' age ranged between 44 and 78 years with a mean age of 58±8.4 years. Post-intervention assessment showed improved depressive symptoms; 50% of the respondents had significantly improved glycaemic control with a statistically significant effect on depression (the median score of PHQ-9 reduced from 6.0 to 3.0). **WAJM 2023; 40(4): 375–381.**

Keywords: Diabetes Mellitus, Depression, Amitriptyline, Glycaemic Control, Medication Adherence.

RÉSUMÉ

La dépression comorbide chez les diabétiques est en augmentation. Elle a été associée à un mauvais contrôle de la glycémie, à un risque accru de complications, à une charge élevée en termes de coûts médicaux et d'utilisation des soins de santé, ainsi qu'à un taux de mortalité plus élevé chez les personnes souffrant de comorbidité. Cette étude a déterminé l'effet de l'antidépresseur (Amitriptyline) sur la dépression et le contrôle de la glycémie chez les patients dépressifs atteints de diabète de type 2 qui fréquentent l'hôpital universitaire fédéral d'Ido-Ekiti (FETHI). Il s'agit d'une étude interventionnelle portant sur 51 patients atteints de diabète de type 2 et déprimés, sélectionnés au hasard à l'aide du questionnaire sur la santé des patients-9 (PHQ-9). Ils ont bénéficié d'une éducation à la santé et ont pris 50 mg d'amitriptyline par voie orale pendant deux mois. L'évaluation post-intervention a été réalisée à l'aide du même outil. L'âge des personnes interrogées était compris entre 44 et 78 ans, avec un âge moyen de 58± 8,4 ans. L'évaluation post-intervention a montré une amélioration des symptômes dépressifs, 50% des personnes interrogées ont eu un contrôle glycémique significativement amélioré avec un effet statistiquement significatif sur la dépression (le score médian du PHQ est passé de 6,0 à 3,0). **WAJM 2023; 40(4): 375–381.**

Mots clés: Diabète sucré, dépression, contrôle glycémique, observance thérapeutique.

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INTRODUCTION

People with diabetes are two-to-three times more likely to suffer from depression in the general population, but this often remains unrecognised and, thus, untreated.[1] The increasing prevalence of DM and associated comorbidities such as depression that is often undiagnosed by the managing physicians leading to poor glycaemic control and premature death[1] that could have been averted or delayed in such patients is of great concern to the researchers and therefore merits being looked into.

Poor adherence to treatment remains a major impediment to improving care, particularly among patients with comorbid diabetes and depression.[2] A cross-sectional study in Palestine found a significant relationship between depression and medication adherence; however, the study showed no relationship between depressive illnesses and glycaemic control among the study population.[2] A similar cross-sectional study done in Nigeria by Idiongesit et al found a significant relationship between depression and medication adherence (p=0.031).[3] Nevertheless, it was observed that depressed diabetic patients do not pay much attention to their daily self-management activities.[4,5] They are likely to have physical limitations and poor quality of life which will eventually affect their self-care behaviour.[4,5]

The root cause of depression is believed to be due to changes in the brain's monoamine neurotransmitters such as serotonin and dopamine which affect mood and behaviour.[6] It is also known that during psychological stress, counter-regulatory hormones such as catecholamines, glucocorticoids, growth hormone, and glucagon are activated and they impede the action of insulin with resultant elevation of blood glucose.[7,8] Conversely, poor glycaemic control and functional impairment due to increasing diabetes complications may worsen depression and lessen the response to antidepressant treatment.[8] In spite of the known devastating effect of depression on diabetes, it was found that only about one-third of patients with diabetes and depression received adequate anti-depressant treatment and very few had adequate psychotherapy over a one-year period.[9,10]

In a systematic review of some pharmacological clinical trials conducted to evaluate antidepressants most suitable for patients with depression and comorbid DM,[11] 68 patients with diabetes and depression were randomly assigned to 8 weeks of treatment with nortriptyline to achieve plasma levels of 50–150 ng/ml. Patients demonstrated significant improvements in mood; however, significant improvements were not observed in glycaemic control.[11] In another study, 60 patients with diabetes and depression were randomly assigned to treatment with fluoxetine (up to 40 mg per day).[9] Treatment with fluoxetine was associated with significant improvement in mood but not glycaemic control.[9,11] On the other hand, Williams et al. assessed whether enhancing treatment for depression would improve mood and glycaemic control in 417 elderly patients (age 60 years and above) with both diseases and found a significant improvement in mood and glycaemic control. Furthermore, a comprehensive review of randomised controlled trials of depression treatment among individuals with diabetes concluded that good scientific evidence suggests that treatments for depression in patients with diabetes are effective.[11,12] Many studies have reported no significant effect of antidepressant medication on glycaemic control in depressed patients with comorbid diabetes mellitus.[11,13,14] Therefore, this study looked at the effect of treatment of mild to moderate depression with amitriptyline in addition to psychotherapy in depressed diabetic patients. The authors chose to use amitriptyline in this study because of its cost effectiveness, availability, and being the most frequently prescribed anti-depressant in the primary care setting where the study was carried out.

METHODS

Study Design

This was an interventional hospital-based study on depression as a comorbidity among type 2 diabetes mellitus patients attending the Family Medicine Practice at FETHI, Nigeria. It was a two-phase study with phase 1 being a cross-sectional study and phase 2 being a 'before and after study design' with a single antidepressant administered to depressed type 2 DM patients to assess outcome on depression and glycaemic control.

Study Population

The study population consisted of all type 2 DM patients who presented at the general outpatient (GOP) clinic within the study period (September to December 2021).

Inclusion and Exclusion Criteria

All consenting type 2 DM patients aged ≥40years and who had been on treatment for at least one month (this was to allow for a minimum of two weeks to fulfill one of the criteria for the diagnosis of depression). Those who were already on treatment for depression or critically ill were excluded.

Sample Size Estimation:

The sample size was determined using Fischer's formula.[15]

$$n = \frac{Z^2 p(1-p)}{d^2} \text{ and } nf = n/1+n/N$$

Where n = the minimum sample size when the population is greater than 10,000; nf = the minimum sample size when the population is less than 10,000; N = the estimated population size in a year (for type 2 diabetes mellitus in 2020 at the clinic = 3600); Z = 1.96 at 95% confidence interval obtained from the standard statistical table of normal distribution; P = estimated prevalence rate of type 2 diabetes mellitus in a given population; 1–P = prevalence rate of type 2 diabetes mellitus in a given population; and D = degree of accuracy desired usually set at 0.05.

From a study on prevalence of depression among type 2 diabetes mellitus patients, Edah JO *et al* reported the prevalence of depressive disorders in diabetic patients as 10.3%, excluding major depression.[14] Hence, an average prevalence of 10% was used to calculate the sample size. Based on the above, sample size (n) = $Z^2p(1-p)/d^2$=1.96 x 1.96 x 0.103(1–0.103)/0.05 x 0.05 = 3.84 x 0.103 x 0.897/0.0025, n = 141.97 = 142. Since the estimated population size was

<10,000, then 'n' above was integrated to 'nf'; nf = n/1+n/N = 142/1+142/360 = 138/1.039 = 136.7.

Given an attrition value of 10% sample size was 150.3 and this was approximated to 150 to the nearest significant figure.

Sampling Technique

Systematic sampling technique was used to recruit respondents among diabetes patients attending the clinic. The GOP medical records of the hospital showed that between 15 and 18 patients with type 2 DM attended the clinic daily, which translated to about 75 patients per week. The GOP clinic runs 5 days in a week so about 300 patients are seen in a month. For the 2 months of the phase 1 of the study, 600 type 2 DM patients were encountered out of which the sample was selected systematically as calculated below:

K=N/n where K= sample interval; N= total number of patients encountered; n= calculated sample size = 600/150 = 4.

This implied every 4th consenting diabetes patient represented the random sample for this study. The first participant was selected by random sampling in the following manner: 4 small pieces of paper were numbered 1 to 4 and an independent patient that was not part of the population sample was asked to randomly pick one out of the 4 folded small papers. The number selected corresponded to the first patient for that day and then every 4th patient was selected.

Research Protocol

The study was carried out in 2 phases. Phase 1 was the first patient contact when the questionnaire was administered and scored. Any of the patients with a score above 4 on the summation of the PHQ-9 was immediately counselled, given health education and placed on oral amitriptyline 50mg nocte (supplied by the researcher) for 8 weeks (the period for establishment of antidepressant effect). A blood sample was collected from all the respondents for the determination of the blood glucose level while only the depressed diabetic patients were re-evaluated in phase 2. The phase 2 started 8 weeks from the day of contact with participants that scored >4 on the PHQ-9 questionnaire when they were re-evaluated. It involved re-administration of the questionnaire and scoring to see if there were any changes in the scores. Blood was collected again for the determination of the blood glucose level. The adherence to the medication was assessed by counting their remaining drugs (oral hypoglycaemic agents and antidepressant) and also with the use of Morisky's adherence tool.

Two research assistants (RAs) were recruited and trained by the investigators for two days for the purpose of data collection, viz-a-viz informed consent process, questionnaire administration and accurate clinical data measurement. The investigators and the RAs took the clinical parameters of the respondents. The phase 2 of the study was carried out by the trained RAs who administered the questionnaire only to those participants on amitriptyline and scored appropriately with the aim of minimizing bias by the researcher.

Data Collection and Instruments

Instruments that were used for data collection included a pre-tested semi-structured interviewer-administered questionnaire drafted in the English Language. The questionnaire was used to obtain relevant information on socio-demographics, duration on medication, current treatment, comorbidity, and certain complications (previous hypoglycaemia, diabetic foot ulcer, diabetic peripheral neuropathy).

The symptoms of depression were determined using Patient Health Questionnaire-9 (PHQ-9), comprising 9 questions to assess the symptoms of depression among the type 2 diabetic patients. The optimal cut-off score for minor depressive disorder is any score above 4 (sensitivity 0.897, specificity 0.989, positive predictive value – PPV 0.875, negative predictive value – NPV 0.981 and overall correct classification – OCC rate 0.973), while that for major depressive disorder is 10 (sensitivity 0.846, specificity 0.994, PPV 0.750, NPV 0.996 and OCC rate 0.992). The cut-off scores are as follows: minimal (0–4), mild (5–9), and moderate to severe (≥10).[15,16]

Adherence was determined using Morisky Medication Adherence Scale (MMAS-4), a 4-item self-report scale developed by Morisky with a high reliability and validity (Cronbach $\alpha = 0.61$) which has been particularly useful in chronic conditions such as diabetes and hypertension. Each item is in a 'yes/no' format with a maximum possible score of 16 implying very poor adherence while 0 is considered good adherence. Each item on the scale is scored 0 to 4 for responses of 'Never, Rarely, Sometimes, Often and Always,' respectively.[17]

The questionnaire was pretested on 15 type 2 diabetes mellitus patients aged ≥ 40 years attending the endocrinology medical outpatient clinic at FETHI who were comparable to sample respondents in socio-demographic characteristics. This resulted in the following benefits: the time taken to complete the questionnaire was established; statements and questions that were misinterpreted were corrected; and the proficiency of the interviewer was verified. This was to ensure thorough standardisation of the data collection method and training of RAs who assisted in the questionnaire administration.

RESULTS

A total number of 150 type 2 DM patients, including 75 (50.0%) men and 75 (50.0%) women were evaluated. The mean age ± SD of patients was 58.7±8.4 years and the median (interquartile range) duration of diabetes was 5 (1.0 – 14) years. Among the patients, 51 (34%) were depressed. The Yoruba tribe accounted for 71.3% and 70.7% were Christian. Majority (130; 86.7%) of the respondents were married with 50% of them residing in a rural area. Majority of the respondents (96; 64%) were from a monogamous family setting while 74% had tertiary education and 0.7% had no formal education. About 30% of the respondents were civil servants.

Table 2 shows diabetes clinical features of both depressed and non-depressed type 2 DM patients. The median duration of diabetes mellitus among the participants was 4.0 years. The presence of co-morbidities and complications among them were found to be statistically significant with

Table 1: Socio-demographic Characteristics of Respondents

Variables	Depressed T2DM (n=51)	Non-depressed T2DM (n=99)	Total (N=150)	χ^2	df	P-value
Age in Years						
Mean ±SD	59.7 ±8.5	58.1±8.2	58±8.4	1.01	148	0.273*
{Min–Max}	(45 – 76)	(44 – 78)	(44 – 78)			
Age Group in years n (%)						
40–49	6(11.8)	13(13.1)	19(12.7)	1.846	3	0.605
50–59	16 (31.4)	41(41.5)	57 (38.0)			
60–69	21(41.2)	32(32.3)	53(35.3)			
70+	8(15.7)	13(13.1)	21(14.0)			
Gender						
Male	22(43.1)	53(53.5)	75(50.0)	1.456	1	0.228
Female	29(56.9)	46(46.5)	75(50.0)			
Ethnicity						
Yoruba	38(74.5)	69(69.7)	107(71.3)	2.236	2	0.327
Ibo	12 (23.5)	22(22.2)	34(22.7)			
Hausa	1(2.0)	8(8.1)	9(6.0)			
Religion						
Christian	39(76.5)	67(67.7)	106(70. 7)	1.950	2	0.458**
Islam	12(23.5)	30(30.3)	42(28.0)			
Traditional	0(0.0)	2(2.0)	2(1.3)			
Marital Status						
Single	0 (0.0)	2(2.0)	2(1.3)	2.164	4	0.764**
Married	43(84.2)	87(87.9)	130(86.7)			
Widowed	6(11.8)	7(7.1)	13(8.7)			
Divorced	1(2.0)	1(1.0)	2(1.3)			
Separated	1(2.0)	2(2.0)	3(2.0)			
Domicile						
Urban Ekiti	27(52.9)	43(43.4)	70(46.7)	1.460	2	0.561
Rural Ekiti	23(45.1)	52(52.6)	75(50.0)			
Outside Ekiti	1(2.0)	4(4.0)	5(3.3)			
Family Type						
Monogamous	30 (58.8)	66(66.7)	96(64.0)	0.899	1	0.343
Polygamous	21(41.2)	33(33.3)	54(36.0)			
Education						
None	1(2.0)	0(0.0)	1(0.7)	3.786	4	0.473
Primary	2(3.8)	10(10.1)	12(8.0)			
Secondary	10(19.6)	16(16.2)	26(17.3)			
Tertiary	19(37.3)	36(36.3)	55(36.7)			
Postgraduate	19(37.3)	37(37.4)	56(37.3)			
Occupation						
C/S	16(31.4)	29(29.3)	45(30.0)	6.757	5	0.239
Artisan	2 (3.9)	16(16.2)	18(12.0)			
Trading	18(35.3)	26(26.2)	44(29.3)			
Farming	7(13.7)	16(16.2)	23(15.3)			
House wife	2(3.9)	1(1.0)	3(2.0)			
Retiree	6(11.8)	11(11.1)	17(11.4)			

**, Independent sample t-test ; **, Fisher's exact test.*

p-values of 0.010 and 0.001, respectively, with > 90% of the depressed having complications. However, the current treatment and drug duration were found not to be significant with a p-value of 0.803.

Figure 1 shows the adherence pattern among the depressed T2DM patients pre- and post- intervention. There was an improvement with an increase in the number of patients with good adherence (high) from 10 patients before the intervention to 30 patients after the intervention.

In Figure 2, the effect of the intervention on PHQ-9 scores which assessed the depressive symptoms is depicted. At the baseline, the median score among the depressed T2DM was 6.0, but with intervention it improved with the median score reducing to 3.0 (p-value of 0.0001).

Figure 3 demonstrates the effect of intervention on Morisky scores which assessed the level of medication adherence. At the baseline, the median score among the depressed T2DM patients was 10.0, and this improved to a score of 2.0 (p-value 0.001).

Figure 4 shows the effect of the intervention on glycaemic control among the depressed T2DM participants. Prior to intervention, 50 of them had poor glycaemic control but with intervention, 50% of them had good control.

Table 3 presents the comparison of the clinical parameters in the depressed type 2 diabetes mellitus patients before and after the intervention. There were statistically significant changes in the blood pressure, glycaemic control (fasting blood sugar), depressive symptoms (PHQ-9 score) and medication adherence (Morisky), with each having a p-value of less than 0.001.

Table 4 displays the predictors of depression among the depressed and it reveals that only poor glycaemic control and poor medication adherence were the identified risks of depression in the study subjects as depicted by p-values of 0.036 and less than 0.001, respectively.

DISCUSSION

Effect of Intervention on Glycaemic Control

The study showed that all the patients in both the depressed group and the non-depressed group had no significant differences in their socio-demographic characteristics. All the depressed T2DM patients were involved in the intervention phase and received an antidepressant medicine for 8 weeks along with psychotherapy. There was an improvement in the post-intervention assessment compared with the baseline. There was an improvement in the PHQ-9 (6.0 vs 3.0) with a p-value of 0.01, which was statistically significant. This showed an improvement in their depressive symptoms and is in agreement with the findings of other studies.[11,15] Similarly, the paired differences in clinical parameters among the intervention group showed

Table 2: Diabetic Clinical Features of Depressed and Non-Depressed Type 2 Diabetes Mellitus Patients

Variables	Depressed (n = 51)	Non-depressed (n = 99)	Total (N = 150)	χ^2	df	P-value
Drug Duration (years)						
Median (Range)	5.0(1.0–12.0)	4.0(1.0–12.0)	4.0(1.0–12.0)			
< 5	25 (49.0)	54 (54.5)	79 (52.7)	0.412	1	0.521
5 or more	26 (51.0)	45 (45.5)	71 (47.3)			
Current Treatment						
Diet	0 (0.0)	1 (1.0)	1 (0.7)	2.117	3	0.803*
Diet + OHA	51 (100.0)	95 (96.0)	146 (97.3)			
Diet + Insulin	0 (0.0)	1 (1.0)	1 (0.7)			
Diet+OHA+Insulin	0 (0.0)	2 (2.0)	2 (1.3)			
Co-morbidity						
Present	41 (80.4)	59 (59.6)	100 (66.7)	6.551	1	0.010
Absent	10 (19.6)	40 (40.4)	50 (33.3)			
Complication						
Present	48 (94.1)	34 (34.3)	82 (54.7)	48.529	1	<0.001
Absent	3 (5.9)	65 (65.7)	68 (45.3)			

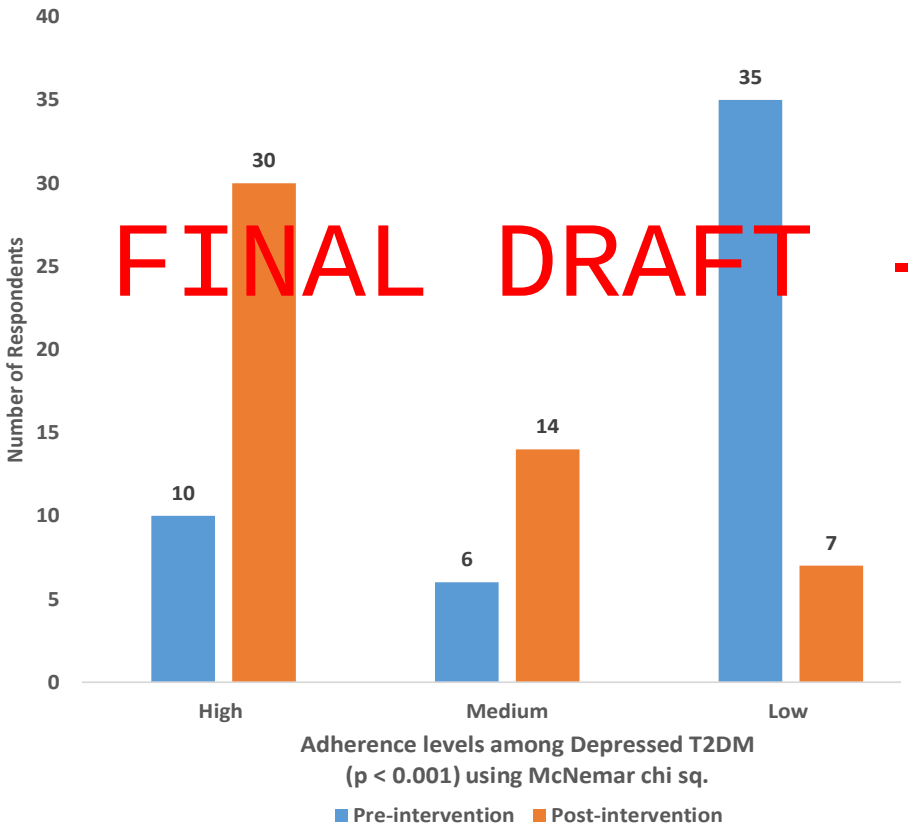

Fig. 1: Showing the Adherence Pattern among the Depressed T2DM Patient Pre- and Post-Intervention. There was an improvement with an increase in the numbers of patient with good adherence (High) from 10 patients before intervention to 30 patients after the intervention.

that the baseline in the glycaemic control was statistically significant. The baseline for the FBS was 8.3±1.5 mmol/L as against the 6.0 ± 0.9 post-intervention (8.3 ± 1.5 vs 6.0 ± 0.9) with a p-value of 0.001. The improved finding in glycaemic control with the treatment of depression in this study is in line with the finding of a study by Khazaie *et al*[9] and that of a systematic review by Roopan and colleagues.[11] Though, HbA1C was used in the latter study, this could not be used in our study due to the high cost and non-availability. Furthermore, 25 of the 50 participants with poor glycaemic control had an improvement with the intervention; this is contrary to the finding in the study of Lustman's as reported in a systematic review by Roopan and colleague[11] in which the intervention with a tricyclic antidepressant (nortriptyline) only brought about an improvement in the depressive symptoms but with no effect in the glycaemic control; however, an improvement in the depressive symptoms could be responsible for the good medication adherence resulting in good glycaemic control observed in this study and as supported by Noman *et al.*[20] This can further be substantiated from the regression of predictors of depression in this study which was statistically significant for glycaemic control as shown in Table 4.

This study also shows a baseline median Morisky adherence score which was found to be 10.0 but got improved by reducing to 8.0 with intervention and with a p-value of 0.001 signifying statistical significance. The adherence pattern among the depressed T2DM patients pre- and post-intervention in this study shows that there was an improvement with an increase in the number of patients with good adherence (high) from 10 patients before intervention to 30 patients after the intervention. Barnard and colleagues,[13] in a randomised controlled trial of a simple, brief intervention integrating treatment of type 2 diabetes and depression, successfully brought about an improved outcome in primary care.[11,14] In the binary regression of this study, poor adherence was found to be statistically significant as a predictor for depression among the diabetes patients with a p-value of 0.001. The reason for this could be the result of an indirect influence; that is, depression leading to poor adherence and poor medication adherence as a result leading to more depressive symptoms in the patient.[11] Furthermore, depression as a comorbid condition in an individual with diabetes is reported to contribute to increased disability, mortality, and significant health burden on patients.[21]

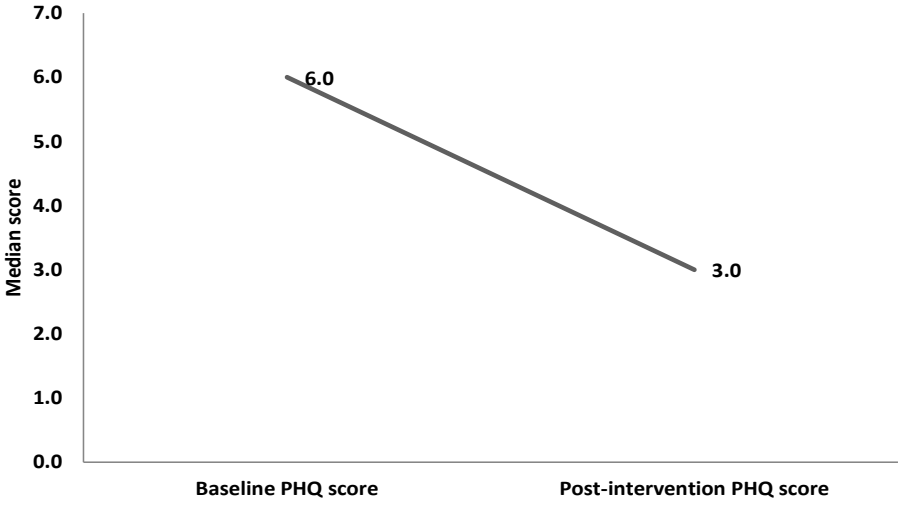

Fig. 2: The effect of the Intervention on PHQ Scores which assessed the Depressive Symptoms.

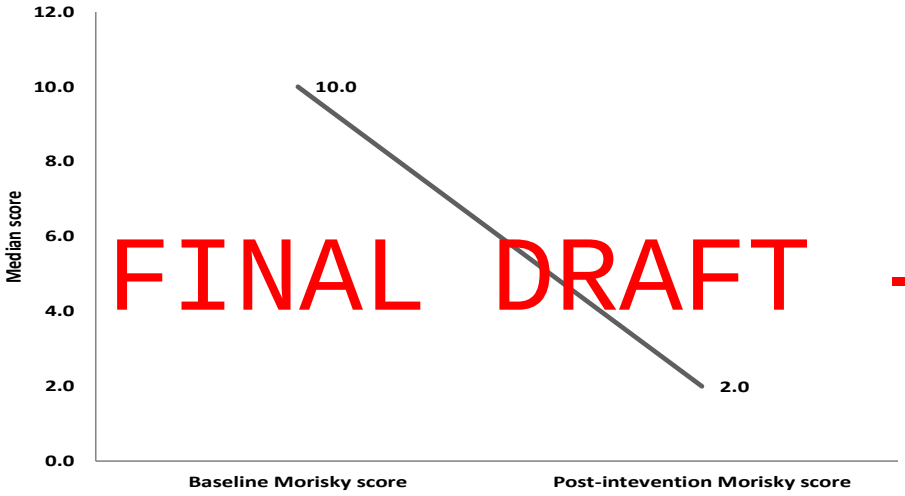

Fig. 3: The Effect of the Intervention on Morisky Scores which assessed the Level of Medication Adherence.

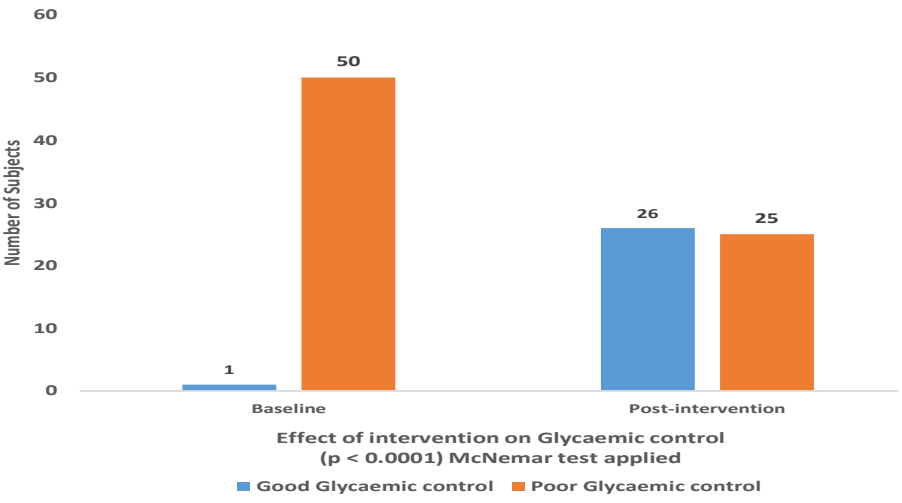

Fig. 4: Bar Chart showing the Effect of the Intervention on Glycaemic Control.

Therefore, an integrated approach to management of depression and type 2 diabetes mellitus is advised to be deployed in real-world practices with competing demands for limited resources so as to bring about an improvement in their care and limit complications that may arise from poor adherence to medication that the dual comorbidity could portend.

ACKNOWLEDGEMENTS

We hereby acknowledge the participants for their cooperation and patience in the course of this study. We also acknowledge the grace of the Almighty God that enabled us to carry the study to a successful end.

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Table 3: Paired differences in Clinical Parameters among Intervention Group

Variables	Mean ± SD	Paired t-test	df	P value
Baseline SBP (mmHg)	134.5 ± 16.4	6.641	50	<0.001
Post-intervention SBP (mmHg)	123.9 ± 10.4			
Baseline DBP (mmHg)	83.3 ± 9.5	5.056	50	<0.001
Post-intervention DBP (mmHg)	76.5 ± 8.7			
Baseline FBS (mmol/L)	8.3 ± 1.5	11.239	50	<0.001
Post-intervention FBS (mmol/L)	6.0 ± 0.9			
Baseline BMI (Kg/m^2)	26.2 ± 3.0	–1.827	50	0.074
Post-intervention BMI (Kg/m^2)	26.5 ± 2.7			
Baseline PHQ	6.0 (5.0–11.0)	–6.265		<0.001*
Post-intervention PHQ	3.0 (1.0 –5.0)			
Baseline Morisky score	10.0 (2.0–16.0)	–6.176		<0.001*
Post-intervention Morisky score	2.0 (0.0–5.0)			

* W*ilcoxon signed rank test applied*

Table 4: Binary Logistic regression for Predictors of Depression

Variables	B	S.E.	OR (95% CI)	P value
Duration of DM (years)*	0.122	0.113	1.130 (0.906–1.409)	0.278
Co-morbidity				
Present			1	
Absent	0.255	0.789	1.290 (0.275–6.051)	0.747
Complication				
Present			1	
Absent	–1.096	0.89	0.334 (0.058–1.941)	0.222
Baseline BP*				
SBP (mmHg)	–0.023	0.039	0.977 (0.905–1.054)	0.548
DBP (mmHg)	0.038	0.056	1.038 (0.931–1.158)	0.498
Baseline Glycaemic control				
Good (≤ 6.0 mmol/l)			1	
Poor (> 6.0 mmol/L)	2.534	1.209	12.609 (1.180–134.713)	0.036
Baseline BMI (Kg/m^2)*	0.069	0.116	1.071 (0.853–1.345)	0.555
Baseline Morisky score*	–0.928	0.211	0.395 (0.262–0.598)	<0.001
Constant	1.020	4.850		0.833

**Variables entered as continuum.*

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