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PHARMACOECONOMIC ANALYSIS OF VILDAGLIPTIN VS GLIMEPIRIDE AS ADD-ON TO METFORMIN IN THE MANAGEMENT OF TYPE 2 DIABETES AT UNIVERSITY OF PORT HARCOURT TEACHING HOSPITAL, NIGERIA

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ABSTRACT

Background: Type 2 diabetes is a chronic metabolic disease that has been identified as a global public health challenge. The cost of controlling glycemic levels with antidiabetic agents is increasing, and there is a need in clinical practice to consider the cost of achieving a target glycemic level. **Aim:** To compare the cost-effectiveness of vildagliptin-metformin vs glimepiride-metformin combination therapies for patients who were inadequately controlled with metformin. **Materials and method**: A retrospective study design using a descriptive approach was adopted to determine the cost effectiveness of the two drug combinations for achieving adequate glycemic control. Data were extracted from the patients' folders using a distinctive data collection form and were used to estimate the cost and extent of glycemic control achieved by the two treatment therapies. Cost effectiveness analysis was done by calculating the expense incurred on 1mmol/L reduction in fasting blood glucose levels after 3 years of therapy and was used to calculate the average cost effectiveness ratio (ACER) and Incremental cost effectiveness ratio (ICER). Data were analyzed using the Statistical Package for Social Science (SPSS) version 28.0 and Microsoft Excel. **Results:** A total of 203 patients were included in the study, out of which 63.1% were females and 36.9% were males. The mean FBG for glimepiride-metformin before the therapy was greater than the mean fasting blood glucose (FBG) after treatment (9.22 ± 2.68 vs 6.76 ± 3.25) ($p<0.01\%$) and same was evident in vildagliptin-metformin (10.48 ±3.59 vs 7.74 ±3.92). There was no significant change in weight levels between the groups. ACER of vildagliptin-metformin therapy compared to glimepiride-metformin therapy was (₦175,357.66 vs ₦129,601.38). Vildagliptin-metformin having an ICER of (₦ 577,359.29). **Conclusion:** Combination therapy with glimepiride and metformin is a very cost-effective therapy for lowering fasting blood glucose (FBG). Vildagliptin, when used in conjunction with metformin, is more expensive but however more effective. Subsidies for the drug should be provided by the government and non-governmental organizations (NGOs).

KEYWORDS: Pharmacoeconomics, Type 2 diabetes, Cost effectiveness, Incremental cost, Incremental effectiveness.

INTRODUCTION

Globally, diabetes is a chronic metabolic disease recognized as a public health challenge characterized by frequent episodes of hyperglycemia (Romesh and George, 2020). Type 2 diabetes accounts for as many as 90% of diabetes mellitus (DM) cases. It is associated with overweight or obesity (in 80-90% of cases); dyslipidemia; increasing age; hypertension; family history; diabetogenic lifestyle (i.e. excessive caloric intake, inadequate caloric expenditure); physical inactivity, polycystic ovarian syndrome, history of gestational diabetes mellitus or delivering a baby with a weight of over 9lb; impaired fasting glucose; depression; schizophrenia; preeclampsia/ gestational hypertension; and also, Covid-19 (Romesh and George, 2020). It is a costly disease that, if not properly managed, can lead to a variety of complications such as retinal, and nephropathic diseases; coronary artery and peripheral vascular disease; and neuropathic complications, which can be devitalizing and fatal.

According to International Diabetes Federation (IDF), the number of people living with diabetes (PLWD) worldwide is predicted to rise from 463 million in 2019 to 700 million by 2045 with alarming social, financial, and health system implications. In Nigeria, the projected prevalence of DM in 2020 among adults aged 20-69 years is reported to be 3% (IDF, 2020). According to World Health Organizations (WHO), Nigeria has the highest number of diabetes cases in Africa, with an estimated burden of 1.7 million which is expected to rise to 4.8 million by 2030 (Andrew *et al*., 2012). Diabetes

imposes a significant economic burden on society (Irgizia et al., 2009) and impedes the achievement of international development goals such as the Millennium Development Goals (MDG). Global diabetes treatment expenditures are expected to rise from $760 billion to $845 billion between 2019 and 2045(IDF, 2019). Diabetes' annual direct costs in Nigeria are estimated to be between $3.5 and $4.5 billion (Suleiman et al., 2015). Diabetes mellitus has been linked to a major cause of morbidity and mortality rate in Nigeria and hence is a serious public health problem. The rising cost of controlling glycemic levels with anti-diabetic agents is a major challenge in managing diabetes and complications associated with the disease which may hamper health budget and national economic development (Oguejiofor et al., 2014). Although many drugs are available for the management of type 2 diabetes mellitus (T2DM), however, finding cost effective drugs for T2DM management has remained a challenge in clinical practice for many years in Nigeria. Vildagliptin and Glimepiride as an add-on to Metformin can be used to manage patients with T2DM who do not respond to metformin alone. Vildagliptin-Metformin has been reportedly used to control and prevent cardiovascular complications (such as myocardial infarction) and retinopathy in patients who are at high risk. HbA1c has also been controlled with Glimepiride-Metformin (Ferrannini et al. 2009).

Cost-effectiveness studies on combination therapies prescribed by World Health Organization (WHO) and other diabetes bodies are rare in Nigeria. Therefore, this study is aimed at comparing the cost-effectiveness of Vildagliptin-Metformin and Glimepiride-Metformin combination recommended by the Diabetes Association of Nigeria (DAN) at the University of Port Harcourt Teaching Hospital, Nigeria.

MATERIALS AND METHODS

This was a retrospective study using a descriptive approach that was conducted at the department of endocrinology outpatient unit of the University of Port Harcourt Teaching Hospital, Nigeria. Ethical approval for the study was obtained from the Institutional research ethics committee. The population of study included all patients with type 2 diabetes mellitus who attended the endocrinology outpatient clinic at any time between 2018-2020 that satisfied the inclusion/exclusion criteria.

Inclusion criteria

Patients aged 20-80 years who failed to achieve glycemic control with metformin monotherapy and were treated with vildagliptin-metformin or glimepiride-metformin combination therapy specified by the Diabetes Association of Nigeria (DAN) at any time from 2018-2020 and had been on treatment for not less than 3months were exclusively used for the study.

Exclusion criteria

Pediatric patients, pregnant diabetic patients, patients on other antidiabetic therapy, and patients with any serious complications such as neuropathy, nephropathy, peripheral vascular disease, foot ulcers, and coronary heart disease during the commencement of therapy were excluded from the study.

Study design

A total of 412 folders were evaluated but only 203 patient folders met the inclusion criteria and were used for the study. The following data were copied out from the case files of the patients: Demographic data, Fasting blood glucose (FBG) level, the weight of the patient, duration of disease, treatment option, diabetic complications, co-morbid disease, and drug-related data. The cost of prescribed drugs was obtained from the pharmacist in the hospital pharmacy using the current hospital drug pricing list.

Cost estimate and analysis

The cost of drugs for each patient was considered taking into consideration the mean daily dose, the strength of the drug, and the treatment regimen for each yearly encounter as documented in the patient folder. The cost determination was done from the Nigerian payers' perspective taking cognizance of only the direct cost which includes the cost of the drugs alone in Nigerian currency (naira).

Cost-effectiveness analysis (CEA)

Cost-effectiveness analysis for both drug combinations was evaluated using the cost and effectiveness data. The average cost-effectiveness ratio (ACER) of both drug combinations and incremental cost-effectiveness (ICER) of both drug combinations were analyzed to arrive at the most cost-effective treatment option. The ICER is calculated based on the incremental cost to clinical outcome: ICER = incremental cost/ effectiveness. This was interpreted using the ICER quadrant plane and decision matrix.

RESULTS

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 28.0 and excel spreadsheet by applying paired student t-test. $P < 0.05$ was considered significant for the study. Descriptive analysis was done, and continuous variables were expressed as Mean ± SD. The data collected from two hundred and three (203) patient folders for the studies were categorized according to the patient demographics.

Table 1: Patient demographics.

Demographics		No of Patient (N=203)	Percentage (%)
Gender	Male	75	36.9
	Female	128	63.1
Age	19-36	19	9.4
	37-54	83	40.9
	55-72	91	44.8
	73-90	10	4.9

Table 1 is the patients' demographic data. Majority of the patients 91 (44.8%) were in the age group of 55-72 years. The female patients 128 (63.1%) were more predominant than the male patients 75 (36.9%).

Table 2: Weight of Patient.

Weight (kg)		N	%
Before therapy	41-80	132	65.0
	81-120	71	35.0
After therapy	41-80	163	80.3
	81-120	40	19.7

Majority of the patients 132 (65.0%) weighed between 41-80 kg given an increase after therapy to a frequency of 163 (80.3%)

Table 3: Comorbidity of patients.

Comorbidity		No of patients (N)	Percentage (%)
Hypertension	Yes	133	65.5
	No	70	34.5
Retinopathy	Yes	5	2.5
	No	198	97.5

From table 3, many co-morbidities are known to associate with diabetes such as retinopathy, congestive heart failure, hyperlipidemia, hypertension, chronic kidney disease, etc. In our study, hypertension 133 (65.5%) was the most prevalent followed by retinopathy 5 (2.5%).

Table 4: Social economic distribution of diabetes patients.

Occupation	Frequency (N)	Percentage (%)
Retired	30	14.8%
Business	81	39.9%
Civil servant	24	11.8%
Housewife	8	3.9%
Famer	11	5.4%
Academia	12	5.9%
Clergyman	13	6.4%
Engineer	8	3.9%
Journalist	4	2.0%
Health officers	12	5.9%

Business inclined patients' (81) were predominant (39.9%) than any other occupation (Table 4).

Table 5: Comparison of patient fasting blood glucose clinical characteristics.

Fasting Blood Glucose(mmol/L)	Drug	Mean±SD	P-value
Baseline vs After 3yrs Therapy	Glim_Met_Baseline	9.22 ± 2.68	< 0.01
	Glim_Met_After 3yrs Therapy	6.76 ± 3.25	
	Vil_Met_Baseline	10.48 ± 3.59	< 0.01
	Vil_Met_After 3yrs Therapy	7.74 ±3.2	
Baseline	Glim_Met_Baseline	8.96 ±2.76	0.017
	Vil_Met_Baseline	10.48 ±3.59	

Glim-Met – Glimepiride-metformin; Vil-Met – Vildagliptin-metformin

Table 6: Comparison of patient weight clinical characteristics.

Weight(kg)	Drug	Mean±SD	P-value
Baseline vs After 3yrs Therapy	Glim_Met_Baseline	73.71 ±12.91	0.03
	Glim_Met_After 3yrs Therapy	75.16 ± 14.72	
	Vil_Met_Baseline	70.94 ±13.13	0.21
	Vil_Met_After 3yrs Therapy	69.68 ± 9.70	
Baseline	Glim_Met_Baseline	73.62 ±14.69	0.299
	Vil_Met_Baseline	70.94 ±13.13	

Glim-Met – Glimepiride+metformin; Vil-Met – Vildagliptin+metformin

Table 7: Comparisons of ICER of add-on therapy at 3years.

Group	Cost for 3yrs treatment (₦)	FBG Base (mmol/l)	FBG Review (mmol/L)	Average reduction (% mean change)	ACER (cost/ average reduction) (₦)	IC	IE	ICER
Vil + Met	480,480	10.48 ±3.59	7.74 ±3.92	2.74	175,357.66	161,660.6	0.28	577,359.29
Glim + Met	318,819.4	9.22 ±2.68	6.76 ±3.25	2.46	129,601.38	-	-	-

ACER – Average Cost Effectiveness Ratio; IC – Incremental Cost; IE – Incremental Effectiveness; ICER – Incremental Cost Effectiveness Ratio

DISCUSSION

Diabetes is a chronic disease that requires continual medical care to reduce the risk of long-term complications, therefore there is a need to understand the relative cost-effectiveness of the prescribed drugs in planning to achieve the desired therapeutic goals more efficiently with minimal financial constraints to the patient. A comparative evaluation based on scientific analysis rather than the apparent cost of the therapy helps the decision-makers choose a more cost-effective treatment options, especially for patients in developing countries with struggling economies like Nigeria. Primary health care physicians deal with patients from varied strata and in a country like Nigeria a large part of the patient population have poor socio-economic backgrounds. Hence cost-effectiveness becomes an even more important deciding factor in clinical practice. Combination therapies are largely prescribed by physicians recently, who believe in aggressive control of the blood sugar.

From the results obtained, the age wise distribution of diabetes was evaluated from a total of 203 patients' folders which met the inclusion criteria that included 128 women (63.1%) which were more predominant than 75 men (36.9%) which was comparable to the study carried out in Uyo. Majority (81) of the patients were into business (39.9%) followed by retired workers 30(14.8%) and civil servants 24(11.8%). This social-economic distribution is probably linked to the sedentary lifestyle disposition of these individuals. Before the therapy began 132 patients had a weight range of 41- 80kg (65.0%) and after three years, 163 patients had weight range of 41-80 kg (80.3%). Hypertension was found very common in 133 patients (65.5%) while retinopathy had a rate of (2.5%). Several studies have shown that diabetes and hypertension frequently co-exist, this was stated to be due to the overlap between their etiology and disease mechanisms, which obesity; inflammation; oxidative stress, and insulin resistance were thought to be the major pathway (Bernard & Chao, 2012).

Among the combination therapies, glimepiride (74.9%) was highly prescribed as add-on therapy to metformin compared to vildagliptin (25.1%) in 51 patients. These findings might be due to the lowered availability of vildagliptin-metformin combination drug at the hospital or due to physicians' preference for patients' glycemic control. Comparison of mean weight reduction of the drug combinations of the patients before and after therapy showed a significant difference with Glimepiride-metformin combination (p-value 0.03) while Vildagliptin-metformin combination was not significant (p-value 0.21). This conformed with a study by Tandon *et al.,* (2019).

Cost-effectiveness analysis is one of the most applied forms of economic analysis in drug therapy. It determines the cost variation between different therapies with similar results in a particular therapeutic area. The main purpose of pharmacoeconomic analysis is not to directly alter the therapeutic decisions of the physicians, but to help the physicians, pharmacists, and policy makers to make informed decisions about whether the cost and extra benefits of the new drug are meaningful within the given budget. To determine the most cost-effective combinations of the two therapies, the study applied various techniques of economic analysis. The ACER and ICER were calculated. The treatment option with the lowest ACER was selected as the best therapy since it demonstrates that the treatment model's denominator, effectiveness, was high and it had a lower cost per unit of effectiveness. Glimepiride as add-on to metformin was more cost effective with an ACER of 129,601.38 as against vildagliptin as add-on to

metformin with an ACER of 175,357.66. Although the ACER is useful in decision-making, the incremental cost effectiveness ratio (ICER) provides more meaningful information. The additional cost incurred by the alternate therapy to obtain extra glycemic control was determined by ICER. The incremental cost effectiveness ratio (ICER) is a cost effectiveness analysis statistic that is used to measure the cost effectiveness of a health-care intervention. The result was based on the ICER quadrant plane and ICER decision matrix and was calculated using the ICER formula.

Considering reduction of FBG, statistical analysis of comparison of mean FBG reduction of the drug combination was done, in which there was a significant difference between the FBG level of the patient before and after glimepiride +metformin (<0.01) and Vildagliptin+metformin (<0.01). However, glimepiride+ metformin was more cost effective than Vildagliptin+metformin having an ICER of 577359.29. This result contrasts with another study carried out in Greece (Kousoulakou *et al.*, 2017) but in line with (Tandon *et al*., 2019).

The study underlines the relevance of evaluating the cost effectiveness of treatment regimens, as primary care physicians caring for economically underprivileged patients must know if a certain regimen is also cost effective in addition to being an effective option.

CONCLUSION

To ensure that diabetes patients receive cost-effective treatment, pharmacoeconomic evaluation should be encouraged. Glimepiride-metformin combination therapy, according to our findings, is a very cost-effective therapy for lowering fasting blood glucose (FBG). Vildagliptin as an add-on to metformin is found to be more expensive although more effective, necessitating an incremental analysis. As a result, glimepiride-metformin should be used. If vildagliptin is made easily accessible and affordable to patients, it will significantly aid in diabetes management. Furthermore, to help patients receive a more effective treatment with Vildagliptin as an add-on to metformin, we recommend that the government and non-governmental organizations (NGOs) intervene by subsidizing the drug.

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