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Drug Utilization Review of Anti-Diabetic Medications and Therapeutic outcome in type 2 Diabetes in a Tertiary Hospital in Northern Nigeria

Comfort O. Olurishe[1], Steven S. Gyang[2], Temidayo O. Olurishe[3], and Titus T. Shekarau[1]

[1]Pharmacy Department, Ahmadu Bello University Teaching Hospital, Shika-Nigeria
[2]Department of Clinical Pharmacy, University of Jos, Jos-Nigeria
[3]Department of Pharmacology & Therapeutics, Ahmadu Bello University, Zaria-Nigeria

Corresponding Author: Comfort O. Olurishe
e-mail: comfortolurishe@yahoo.com Telephone : +234 802 355 0257

ABSTRACT

Background: Attainment of therapeutic goals in Type 2 Diabetes Mellitus (T2DM) necessitates the rational use of drugs, given the wide options available and the presence of co-morbid diseases.

Objectives: To evaluate the drug utilization parameters and short- term outcome of pharmacotherapy in T2DM patients attending a tertiary hospital in Northern Nigeria.

Methods: Data was obtained from the folders of outpatients that attended clinic between June 2010 and June 2011 using a structured proforma and analyzed with descriptive statistics and chi square.

Results: The mean number of drugs per prescription was 5.29 ± 0.09, while drugs prescribed from the Essential Drug List were 48.1%. Generic, proprietary prescriptions and fixed dose combinations were 66.72%, 33.27% and 5.91% respectively. The number of encounters with an injection and an antibiotic, were 18(16.38%) and 19 (17.27%) respectively. There was a therapy change in 71.9%, whereas 29.1% had a same drug same dose prescription. Metformin-glibenclamide therapy was most utilized (53.27%). There was no statistically significant difference between the outcome of therapy in patients with initial poor glycaemic control and those with optimum glycaemic control. Hypertension was the commonest co-morbid disease (86.1%) with angiotensin converting enzyme inhibitors being most prescribed (72.52%) antihypertensive drugs.

Conclusion: Utilization of anti-diabetic agents was rational. However outcome of therapy in patients studied could still be improved by close monitoring of patient factors that may affect efficacy and encouraging patients' adherence.

Key words: Drug utilization, Type 2 diabetes mellitus, Metformin-glibenclamide therapy

INTRODUCTION

There has been a gradual and continuous increase in rural-urban migration, particularly in Sub-Saharan Africa. With this migration comes an apparent shift in lifestyle from a relatively healthy traditional pattern, to the urban scenario of increased quantity and reduced quality of food, physical inactivity, smoking and increased alcohol indulgence[1]. These are all risk factors for the development of diabetes mellitus, more so urbanization has been described as a major factor increasing diabetes prevalence in Africa[2]. Type 2 Diabetes mellitus (T2DM) is a chronic metabolic disorder affecting virtually every cell in the body leading to pathology in multiple organ system with consequent high health care resource expenditures. In a study in 2010 to estimate the Global prevalence of diabetes, the result revealed an overall total predicted increase in diabetes from 2010 to 2030 as 54%, at an annual growth of 2.2%, which is nearly twice the annual growth of the total world adult population[3]. Diabetes is also seen to seemingly be the world's most threatening epidemic, which is beginning to submerge the developing world[4]. The potential severity of diabetes is such that epidemiologists have predicted that its economic impact and death toll will surpass the ravages of HIV and AIDS in the near future. Recently,

the World Health Organization (WHO) stated that more than 80% of diabetes deaths occur in low and middle income countries and projected that diabetes deaths will double between 2005 and 2030[5]. Another study in a tertiary hospital in Nigeria also showed that Diabetes admissions accounted for 15% of all medical admissions and 22% of all medical deaths[6]. In Sub Saharan African, there is an early decompensation of this disease leading to various complications due to late diagnosis, inequalities in accessing care[7] and irrational use of drugs. The forecast of increase prevalence in coming years inevitably translates to an increase in the prescription volume of anti-diabetic drugs. Though proper patient education, lifestyle modification and diet, play key roles in the overall management of T2DM, in the majority of subjects, type 2 diabetes is usually not well controlled by lifestyle modifications.

As such, the place of drug therapy cannot be overemphasized presenting major challenges to health care delivery systems. It is also very apparent that diabetes in Africa is associated with a high complication burden, which is not just difficult to treat but also to prevent[1]. However, ensuring rational use of drugs would go a long way to prevent decompensation of the disease, development of complications and improve the quality of life of the patient.

The evaluation of drug use in health care systems for the purpose of promoting rational use of drugs is through drug utilization reviews (DUR). Drug use review is important as it provides insight into the efficacy of drug use[8] and documents the extent of inappropriate prescribing and dispensing of drugs [9]. It also reveals if drug use meets predetermined criteria for treating specific diseases like T2DM. In underdeveloped and developing countries DURs are yet to be fully incorporated into the system as a tool to improve the rational use of drugs. In Health facilities where drug reviews are done routinely and have become an established part of the system, opportunities exist to make interventions to improve rational use of drug. The rational use of drugs also becomes very important especially in the management of diseases like T2DM where there is an increasing number of ways to attack the cardinal metabolic defects (insulin resistance and beta-cell failure) of the disease. These numerous possibilities i.e. drug agents for pharmacological interventions leave patients, pharmacists and doctors with the task of selecting from an armamentarium of anti-diabetic agents. Clinical effectiveness and attainment of set therapeutic goals therefore implies the rational use of these drugs. Moreover, as the patterns in the use of anti-diabetic agents is changing enormously around the world, it is essential to conduct an investigation into the trends in this tertiary care facility where DUR has not been sufficiently explored in describing pattern of drug use with the aim of promoting and ensuring rational use of drug. This will allow maximum benefits from pharmacological agents with improved prognosis, reduced economic, social and financial burdens of the disease. The objective of this study is to evaluate the drug utilization parameters associated with pharmacotherapy of Type 2 Diabetes Mellitus among diabetic patients in a tertiary institution and to assess the short-term outcome of drugs usage.

MATERIALS AND METHODS

Study Design/Setting

A retrospective drug utilization evaluation involving the use of randomly selected case files of diabetic patients attending the Medical out Patient Clinic of a tertiary institution in northern Nigeria over a one-year period between June 2010 and June 2011. Patients who had been freshly diagnosed diabetic i.e. less than one year and patients who were not regular with clinic appointments were excluded from the study. The WHO recommended procedure for drug utilization evaluation was then employed to analyze the drug-use parameters for the disorder Type 2 Diabetes Mellitus[9].

Data collection

Case folders of one hundred and ten patients attending the out-patients diabetic clinic were used. A proforma form was designed and relevant data such as demographics of patient, prescribing and facility drug use indicators and details of drug usage were extracted. Fasting blood glucose (FBG), 2 hours post prandial (2HPP), blood pressure, therapy changes, co morbidities and their treatment /complications and hospitalization were also obtained from the patients' case folders. FBG and 2HPP on subsequent visit and at the end of the study were also used as indices for monitoring therapy.

Data Analysis

All data obtained was entered into the SPSS version 11 software which was used for all the statistical analysis. Results of the study were expressed as mean or percentage. The differences between variables were analysed using Chi-Square test. P values of 0.05 or less were considered statistically significant.

RESULTS

1. Demographics of patients: In this study there was a higher incidence of Diabetes in patients aged 51 60 yrs (42.7%). Male patients in study were 33.6% while Females were 66.4%. There was no statistically significant difference in the number of female patients hospitalized compared to males P>0.05 (Chi square). Most patients in the study were housewives (49.1%) accounting for almost half of the total number of patients in study. This was followed by civil servants (21.8%) and businessmen (11.8%). (33.7%) had diabetic history of less than 5 years and 27.8% had greater than a 10 year history.

2. Prescription Pattern of Antidiabetic Agents: Combination of Sulphonylureas and biguanides was the major line of therapy employed (53.27%) with Metformin/Glibenclamide dual therapy accounting for 42.7% of antidiabetic medications while 13.62% of the patient were on insulin preparations (Table 1).

Table 1: Antidiabetic agents prescribed

Antidiabetic agents	Percentage of patient
Sulphonylureas	1.81
Biguanides	10
Sulphonylureas/ Biguanides	49.09
Sulphonylureas/ biguanides/glitazones	17.27
Fixed dose(Sulphonyl Ureas/Biguanides)	8.18
Insulin	2.72
Insulin/oral hypoglycaemic agents	10.90

3. Prescribing and Facility Indicators. Number of drugs prescribed was between 3 and 7 with 36.4% of patients having 6 drugs per prescription. Average number of drugs per prescription was 5.29 ± 0.098. Prescriptions for Injections and antibiotics were 16.38% and 17.27% respectively (Table 2). All anti-diabetic medications in the EDL were available in this facility.[16]

Table 2: Drug use indicators

Core Indicators	n(%)
Total Number of Drugs prescribed	592
Average Number of drugs per prescription	5.29±0.098
Number of encounters with an injection	18 (16.38%)
Number of drugs prescribed from the EDL	48.1%
Number of encounters with an antibiotic	19 (17.27%)
Number of drugs prescribed by generic name	395(66.73%)
Number of drugs prescribed by proprietary names	197(33.27%)
Number of fixed dose combinations	35(5.91%)
Availability of EDL	Yes
Key drugs availability	100%

4. Outcome of therapy in patients: There was no statistically significant difference p>0.05 (Chi-square) in treatment outcome when patients that had an initial poor glycaemic control were compared with those with starting optimum glycaemic control (Figure 1) where Optimum glycaemic control level is (FBG 4.5-6.7 and 2hpp <10), Acceptable glycaemic control is (FBG 5-8 and 2hpp >9) and Poor glycaemic control is (FBG >9 and 2hpp >10)[18]. However, about 50% of patients who had poor glycaemic control at the beginning of the evaluation period had a satisfactory glycaemic control level at the end. Likewise, 76.34% of patients with satisfactory glycaemic control at the beginning of the evaluation still remained at this status of glycaemic control at the end of the study.

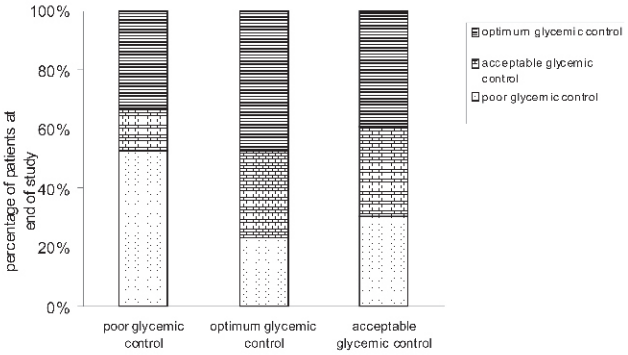

Figure 1: Changes in GC at the end of evaluation period with respect to baseline GL

No statistically significant difference p>0.05 (Chi-square) in treatment outcome comparing patients with initial poor glycaemic control with those with starting optimum glycaemic control

Key:
GC- Glycaemic control, GL Glycaemic level, GCL Glycaemic control level, OGC- Optimum glycaemic control, PGC- Poor glycaemic control, AGC- Acceptable glycaemic control.

4: Medication Switch in Patients: Medications were switched once in 29.1% of patients, twice in 16.4%, of patients and 3.6% had their medication switched three to four times during the one year study period. Doses of the antidiabetic medications were increased in 9.1% of the patients, decreased in 2.7% and titrated in 7.3% of the patients. Totally, therapy change **was seen in 71.9% of patients;** while the remaining 29.1% of

patient had a same drug same dose (SDSD).

5. Co-morbid Diseases and Management in Patients: Hypertension was the major co- morbid disease (86.1%) followed by infections (19.09%) (Table 3). Also 25.45% of patients in addition to having hypertension as a co-morbid condition also suffered from one other co morbid disease and 10.9% from two other additional co-morbid conditions. Anti-hypertensives, antibiotics, analgesics and anti-malarials were the most frequently prescribed non- anti-diabetic drugs. ACE inhibitors were the commonest (72.52%) antihypertensive drugs prescribed and aspirin 75 mg was the most frequently prescribed (85.71%) adjunct non-anti-hypertensive drug.

Table 3: Incidence of Co-morbid Diseases

Co-morbid Diseases	Number of Patients	Percentage of Patients
Hypertension	95	86.1
Obesity	10	9.09
Malaria	11	10
Infection	20	19.09
GRD	3	2.72
Erectile dys function	2	1.81
Peptic Ulcer	4	3.63
Thyrotoxicosis	2	1.81
None	13	11.8
Others	7	6.3

DISCUSSION

The female patients in the study accounted for about two third of the total number of patients sampled for the study, most being housewives. This gender distribution in this study is in agreement with earlier studies [10, 11, 12] all of which demonstrated an increasing trend in the number of female diabetic patients. However, more of the male patients were hospitalized during the study period compared to females. They were either diagnosed diabetic on hospitalization, following hyperglycaemic emergencies or had very irregular clinic attendance and so could not be monitored as required. The possible explanation could be because males in this part of the world complain of tight schedules at work leading to negligence of health issues. T2DM was more prevalent in the elderly as similarly reported in a study in Nepal, to determine prescribing pattern in diabetic outpatients in a tertiary care teaching hospital[13]. The prevalence of T2DM in the elderly patients is an increased burden to tissues and organs already being plagued by age. This implies the need for tight glycaemic control and close monitoring in order to reduce the risk of development and progression of complications.

The average number of drugs prescribed per patients was high and was a consequence of other co -morbid disease in the population of patients studied. It is recognized that more drugs are prescribed for diabetic patients, than patients suffering from other diseases[14]. However, these drugs were mainly prescribed generically, and the National Drug Policy using the Essential Drugs List encourages generic prescribing which allows flexibility of stocking thereby increasing accessibility, availability and affordability of various brands of a particular drug. In addition, generic drugs are most often cheaper and equally effective as proprietary brands. In Nigeria, the diabetic patient still has to pay about 72% of the total health care cost on drug prescription, followed by transportation and laboratory tests, which amounts to about 7% of the total cost to the individual[15]. The cost of medications is therefore very important to the diabetic patients. In addition to their diabetic status, these patients incur other healthcare costs including treatment of co-morbid diseases. In order to ensure adherence therefore, the economy of the individual patient must be taken into consideration. The level of generic prescribing in this study is commendable and as such should help in fostering patients' adherence as cost of medication is a common reason given by most patients for non-adherence to medication. Nevertheless this should be without compromising treatment standards which is aimed at attaining optimal diabetic control and set therapeutic objectives.

However, some of the antidiabetic agents prescribed were not in the EDL which was last updated in 2003. The advances in the identification and development of new and unique medications have been on the increase in the last decade, leading to the introduction of new and licensed anti-diabetic agents. These agents which include the glitazones, third generation sulphonylureas and the incretin mimetics are not listed in the EDL and possibly explains the reason for the rather low patronage of EDL drugs. Nevertheless the most utilized medications in this study were listed in the EDL, being sulphonlyureas and biguanide as dual therapy. Triple therapy was also employed where a glitazone was added to sulphonlyurea/biguanide combination especially in patients who showed persistent poor glycaemic control. Insulin therapy was only introduced when oral hypoglycaemic agent failure became imminent, or in the presence of co-morbid diseases which compromised glycaemic

control or in hyperglycaemic emergencies. Similar study reported the major use of dual oral hypoglycaemic agent (OHA) therapy followed by triple oral hypoglycaemic agent therapy and then Insulin/ oral hypoglycaemic agent[17]. Conventionally, a combination therapy is used when monotherapy is no longer able to achieve adequate glycaemic control. The basic rationale of combination therapy is to provide additive or synergistic effects with different molecular mechanisms of action and to allow employment of lower doses for the disease management. Such lower doses reduce the risk of adverse effect thus ensuring patients' safety. The WHO step care approach of management of T2DM[18] and a consensus algorithm for the initiation and adjustment of therapy in T2DM[19] states that if glycaemic control is not achieved in spite of lifestyle modification and dietary measures, treatment should be initiated with a sulphonylurea or biguanide. It further states that if glycaemic control is still not achieved a combination therapy of a biguanide and sulphonylurea should be used.

The management strategy employed in this institution for managing patients withT2DM is acceptable following the step care approach as outlined by the WHO and the Nigeria National Standard Treatment Guidelines for the management of T2DM. Though no significant difference in treatment outcome in patients with initial poor glycaemic control compared to those with starting satisfactory control, patients with poor glycaemic control at the beginning of the evaluation period had been reduced by about 50% at the end of the study period This implies that the outcome of therapy met stated goals in this category of patients as most of them who still ended up with poor glycaemic control did not comply with drug therapy. Achieving this level of success has been as a result of therapy changes with reference to glycaemic control levels and close monitoring of patients. Though the results on therapy change contrast the findings in a study on utilization of oral hypoglycaemic agents in U.S.A.[20], optimizing glycaemic control is influenced by therapy changes as well as patient adherence to prescribed drug regimens.

The core components of diabetes care involve the prevention of hyperglycaemia, treatment of co-morbid diseases, and prevention and management of macrovascular and microvascular complications. In people with diabetes mellitus, hypertension is associated with insulin resistance and abnormalities in both the renin-angiotensin system and sympathetic tone, which result in vascular and metabolic consequences that contribute to morbidity. Hypertension was the commonest co morbid disease in this study, as such management of diabetic hypertensive patients was also considered, as a well controlled blood pressure in T2DM patients is pivotal to prevention of cardiovascular and other macrovascular complications[21]. The hypertensive patients were mostly treated with angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), in contrast to a study in Western Nigeria in 2007 where slightly above 50% received ACEI and ARBs as part of their treatment [22]. This difference could be linked to an increase in awareness and adherence to current blood pressure management guidelines. This guideline recommends the use of ACE-I and ARBs for management of hypertension in diabetic patients either singly or in combination with other antihypertensive drugs depending on the blood pressure[23]. Patients that were not hypertensive were also placed on ACE-I as a renoprotective agent and aspirin 75 mg. Low dose aspirin (75 mg) is recommended in diabetes as prophylaxis against thromboembolism. It is now well established that ACE inhibitors have reno-protective effects that may offer benefit over and above the benefits of blood pressure control alone[24]. Patients with diabetes should achieve a target blood pressure of less than 130/80 mm Hg[25] and the number of diabetic hypertensive patients in this study, who had satisfactory blood pressure values at the beginning of the evaluation period had increased at the end. This increase is of importance considering the number of patients whose risk of developing complications had been reduced.

Infections, malaria and obesity were also common in the patients population which was also similar to previous studies in Nigeria [10,26]. Individuals with diabetes have a greater frequency and severity of infections[27] leading to considerable morbidity and mortality in patients. This is because the ability of the skin to act as a barrier to infection may be compromised when the diminished sensation of diabetic neuropathy results in unnoticed injury. Hyperglycemia and acidaemia also exacerbate impairments in humoral immunity, polymorphonuclear leukocyte and lymphocyte functions, causing infections to thrive easily[28] resulting in a fast decompensation of the disease. The infections seen in patients included respiratory tract infections, genito-urinary tract infections, gastrointestinal infections and fungal infections. Various antibiotics and antifungal agents were prescribed in this study as

treatment measures for patients following culture and sensitivity testing. The high incidence of malaria infection shows the endemicity of malaria in this region necessitating the high number of antimalaria prescription observed, mainly the artemisinin- based combination therapies.

CONCLUSION

Pharmacotherapy of T2DM in this institution was seen to largely be in line with the National Standard Treatment Guidelines and step care approach recommended by WHO. The outcome of therapy in most patients also met with stated goals. However with the emergence of new and novel therapeutic agents, future management of patients with diabetes should incorporate these new agents in addition to more rational and efficient use of existing ones.

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