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PHARMACOECONOMICAL EVALUATION OF ORAL HYPOGLYCEMIC AGENTS FOR TYPE-2 DIABETES MELLITUS IN A MULTISPECIALITY HOSPITAL

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ABSTRACT: The objective of the study was to determine the cost effective drug among oral hypoglycemic agents utilized in a multispeciality hospital to treat type-2 diabetes mellitus. The prospective cost effectiveness study was conducted for 6 months period in patients who were diagnosed with type-2 diabetes mellitus and were receiving treatment specifically with oral hypoglycemic agent(s). The data obtained was introduced to Incremental Cost Effectiveness Ratio determination to arrive at the most cost effective drug and the prescription pattern and drug related problems in the patients were monitored. A total of 141 patients were included in the study. Glipizide among monotherapy ($p<0.01$), Glimepiride as add on therapy to Metformin ($p<0.001$), fixed dose triple combination of Glimepiride, Pioglitazone and Metformin ($p<0.01$) and fixed dose combination of Glimepiride and Metformin ($p<0.001$) were found to be more effective using statistical analysis. Most of the patients were receiving fixed dose combinations (43.6%) out of which Glimepiride and Metformin combination (34.42%) was predominant over the others. Serious drug interactions (12) and adverse drug reactions (5) were monitored. For Type 2 Diabetes Mellitus, Metformin among monotherapy, Glimepiride as an add on to Metformin, fixed dose triple combination of Glimepiride, Pioglitazone and Metformin can be considered as the best drug of choice with respect to cost effectiveness.

INTRODUCTION: Diabetes is a modern-day epidemic and is rightly recognized as a global public health issue. India leads the world with the largest number of diabetic subjects earning the title termed the "Diabetes capital of the world". According to the Indian Council of Medical Research (ICMR), in a national diabetes study, India currently has 62.4 million people with diabetes.

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Prevalence of diabetes among adults has reached approximately 20% in urban and approximately 10% in rural populations in India [1]. The disease appears to be more prevalent in the south of the country as compared to the northern and eastern parts [2].

In a developing country like India, 85% of total health expenditures are financed by house-hold out-of–pocket expenditure. Many poor people frequently face a choice between buying medicines or buying food or other necessities due to limited resources and high pricing of drug. The cost effective analysis of the oral hypoglycemic agents will reduce the healthcare burden on patients with Diabetes mellitus and reduces the total health expenditure of the country [3-5].

Pharmacoeconomics determine the costs and outcomes associated primarily with pharmaceuticals address different decision problems, including cost–utility analysis (CUA), cost-effectiveness analysis (CEA), cost minimization analysis (CMA) and cost–benefit analysis (CBA). Pharmacoeconomics is now more than ever before at the leading edge of thinking in terms of securing the most rational and efficient use of scarce health-care resources for diabetes [6, 7]. The aim of this study was to determine the most cost-effective drug among oral hypoglycemic agents utilized in a multi-specialty hospital. Other objectives of the study were to monitor prescription pattern and drug related problems with oral hypoglycemic agents.

MATERIALS AND METHODS: This Prospective Cost Effective Study was conducted for 6 months in both inpatients and outpatients of Cardiology, General Medicine and Nephrology Departments with Type 2 Diabetes Mellitus in a 300 bedded multispecialty hospital located at Elayampalayam. The study was approved by the Institutional Ethical Committee of Vivekanandha Medical Care Hospital. About 383 Type 2 DM patients were interviewed and based on inclusion and exclusion criteria, 141 patients were recruited in our study after getting the patient consent and the required data were collected in specially designed data entry form.

The study was included with patients of age between 20 – 80 years in both genders, having Type 2 Diabetes Mellitus prescribed with oral hypoglycemic agents. We excluded patients with age < 20 and > 80 years, Pregnancy and Lactation, patients on insulin therapy, patients with lifestyle modification alone and patients not willing to repeat glucose monitoring from the study. The collected data were analyzed and the adherence level of the patients was categorized into low, medium and high adherence by using Morisky 8–Item Medication Adherence Scale.

The drug interactions in the prescriptions were checked out by using LEXICOMP Software. The adverse drug reactions were monitored and assessed using Naranjo Causality Assessment Scale.

The data was interpreted using ICER quadrant plane and the report was developed using ICER decision matrix.

Statistical Analysis: The statistical analysis was done using Graph Pad Prism version 6.07. The HbA1C level before and after the drug treatment was expressed as Mean ± SD. Paired student t- test was used to analyze the statistical difference between the HbA1C reductions with various oral hypoglycemic agents. $p<0.05$ was considered as statistically significant.

RESULTS:

Patient demographics: The data collected from 141 diabetic patients were analyzed and categorized according to the patient demographics. The mean age of the study population was 57.36 ± 11.49 years (range 20-80 years), where the maximum number 47 (33.3%) of patients were in the age group of 61-70 years. The male patients 77 (54.6%) were more predominant than female patients 64 (45.4%). (**Table 1**)

TABLE 1: PATIENT DEMOGRAPHICS

Demographics		No of Patients (n=141)	Percentage (%)
Gender	Males	77	54.6%
	Females	64	45.4%
Age	20-30 Years	01	0.7%
	31-40 Years	13	9.0%
	41-50 Years	21	14.8%
	51-60 Years	45	31.9%
	61-70 Years	47	33.3%
	71-80 Years	14	9.9%
Mean Age		57.36 ± 11.49 Years	

Co- Morbidity Assessment: The patients having normal Body Mass Index (BMI) 68 (48.2%) were more predominant than overweight 48(34.1%) and underweight 11(7.8%) patients. About 48 (34.05%) of patients in the study were having prior family history of diabetes. The co-morbidities like hypertension, hyperlipidemia, Congestive Heart failure and Chronic Kidney Disease co-exist with Diabetes Mellitus, out of which Hypertension (47.5%) was more predominant. Among the other co-morbidities hypothyroidism 13 (32.5%) was the major followed by Chronic Obstructive Pulmonary Disease 9 (22.5%). (**Table 2**)

TABLE 2: CO- MORBIDITY ASSESSMENT

Co - Morbidity	No of patients (n=141)	Percentage (%)
Hypertension	67	47.5%
Hyperlipidemia	11	7.8%
Coronary heart disease	6	4.3%
Chronic kidney disease	17	12.1%
Hypothyroidism	13	32.5%
Asthma	8	20%
Angina	6	15%
COPD	9	22.5%
Depression	4	10%
Others	40	28.3%

COPD – Chronic Obstructive Pulmonary Disease

Pharmacist Workup on Drug Therapy: Out of 141 patients selected for the study, 124 (87.94%) of patients were outpatients and remaining were inpatients 17 (12.05%). According to Morisky 8 – Item Medication Adherence Scale, about 72 (51.08 %) of the diabetic patients in the study were highly adherent to the drug therapy, 41 (29.07 %) were moderately adherent and remaining 28 (19.85 %) were having low adherence. About 116 (82.26%) number of the patients were in regular follow up of diabetic treatment. Out of 141 patients, 95 (67.37%) of the patients selected for the study were affected by diabetes for more than 4 years. Only 102 (72.34%) of the patients in the study were strictly adapted to their lifestyle modifications. 61(43.26%) of the patients were prescribed with fixed dose combinations, followed by monotherapy 35 (24.82%). Highly prescribed oral hypoglycemic agents in the selected patients in our study was Metformin among monotherapy in 11 (31.42%) patients, Glimepiride as an add on to Metformin among add on therapy in 15 (45.45%) patients, Glimepiride + Voglibose + Metformin among fixed dose triple combinations in 7(58.33 %) patients, Glimepiride + Metformin among fixed dose combinations in 21 (34.42 %) patients.

About 226 drug interactions were monitored in the prescriptions, 71.68% were moderate, 23% were minor and 5.3% were major interactions (**Fig. 2**). During the study, 5 adverse drug reactions were monitored, out of which 4 were Probable and an ADR was Definite with respect to Naranjo Adverse Drug Reaction Probability Scale. (**Table 3**)

TABLE 3: PHARMACIST WORKUP ON DRUG THERAPY

Characteristics		No:of patients (n=141)	Percentage (%)
Adherence level	Low	28	19.85%
	Medium	41	29.05%
	High	72	51.1%
Regular follow-up	Yes	116	82.26%
	No	25	17.73%
Duration of therapy	<1 year	15	10.63%
	1-2 years	16	11.3%
	3-4 years	15	10.63%
	>4 years	95	67.37%
Lifestyle Modifications	Yes	102	72.34%
	No	39	27.66%
Drug Interactions	Major	12	5.32%
	Moderate	162	71.68%
	Minor	52	23%
Adverse Drug Reactions	Probable	8	5.67%
	Definite	1	0.7%

Incremental Cost Effectiveness Ratio (ICER) Analysis: The incremental cost effectiveness ratio was calculated using ICER formula and the result was based on ICER quadrant plane and ICER decision matrix [8]. Metformin shows the maximum HbA1C reduction among monotherapy. The statistical analysis shows that there was a highly significant difference between the HbA1C level of patients before and after the Glipizide treatment ($p<0.01$) and hence found to be the most effective drug when compared with other drugs among monotherapy.

TABLE 4: COMPARISON OF ICER OF MONOTHERAPY

Drugs	Cost of therapy for 6 months (Rs)	Mean ± SD of HbA_1C		Reduction of HbA_1C	IC	IE	ICER
		Baseline	EOS				
Glipizide	126.00	9.3 ± 0.99	8.8 ± 1.01**	0.5	-	-	-
Metformin	650.16	8.2 ± 1.82	7.1 ± 1.7*	1.1	524.16	0.6	873.6
Glimepiride	628.20	8.8 ± 1.5	8 ± 1.5*	0.9	- 21.96	- 0.2	109.8
Gliclazide	1800.00	7.8 ± 1.6	7.0 ± 1.2*	0.8	1171.8	-0.1	-11718
Pioglitazone	918.00	8.7 ± 1.5	8.1 ± 1.1	0.6	- 882	-0.2	4410
Voglibose	5832.00	9.4 ± 2.2	8.9 ± 1.9	0.5	4914	-0.1	-49140
Sitagliptin	4041	9.6 ± 2.5	9.1 ± 1.8	0.5	- 1791	-	-

EOS - End of Study **IC-** Incremental Cost **IE-** Incremental Effect
ICER - Incremental Cost Effectiveness Ratio **p < 0.01 * p < 0.05

Considering HbA1c reduction, Glibenclamide as an add on to Metformin, shows the maximum HbA1c reduction. The most effective drug was found to be Glimepiride as an add on to Metformin (p<0.001) since there was statistically significant difference between the HbA1C level before and after the drug treatment.

TABLE 5: COMPARISON OF ICER OF ADD ON THERAPY

Drugs	Cost of therapy for 6 months (Rs)	Mean ± SD of HbA_1C		Reduction of HbA_1C	IC	IE	ICER
		Baseline	EOS				
Metformin + Glibenclamide	749.16	9.1 ± 1.6	7.9 ± 1.63**	1.2	-	-	-
Metformin + Glimepiride	1278.36	8.5 ± 1.3	7.5 ± 1.27***	1.4	529.2	0.2	2646
Metformin + Gliclazide	2178.36	8 ± 2.15	7.1 ± 2.10	0.2	900	- 1.2	-750
Voglibose + Pioglitazone	6750.00	9.1 ± 1.9	8.5 ± 1.2	0.63	4571.64	0.43	10631.72
Metformin + Sitagliptin	4691.16	8.9 ± 2.4	8.1 ± 2.12	0.5	-2058.84	-0.13	15837.23

EOS - End of Study **IC-** Incremental Cost **IE-** Incremental Effect
ICER - Incremental Cost Effectiveness Ratio, *** p < 0.001 **p < 0.01

Fixed dose triple combination of Glimepiride, Pioglitazone and Metformin, shows the maximum HbA_1C reduction. The statistical analysis shows that there was highly significant difference between the HbA_1C levels of the patient tested before and after the Glimepiride + Pioglitazone + Metformin (p<0.01) treatment, which was found to be more effective.

TABLE 6: COMPARISON OF ICER OF FIXED DOSE TRIPLE COMBINATIONS

Drugs	Cost of therapy for 6 months (Rs)	Mean ± SD of HbA_1C		Reduction of HbA_1C	IC	IE	ICER
		Baseline	EOS				
Glimepiride + Voglibose + Metformin	221.40	11.3 ± 1.57	10.5 ± 1.95*	0.8	-	-	-
Glimepiride + Pioglitazone + Metformin	4176.00	9.8 ± 1.2	8.4 ± 1.58**	1.4	3954.6	0.6	6591
Metformin + Sitagliptin	4691.16	8.9 ± 2.4	8.1 ± 2.12	0.5	-2058.84	-0.13	15837.23

EOS - End of Study **IC-** Incremental Cost **IE-** Incremental Effect
ICER - Incremental Cost Effectiveness Ratio**,** **p < 0.01 * p < 0.05

DISCUSSION: Diabetes mellitus is a multifactorial metabolic disorder. The main defects include insulin resistance and insulin deficiency [9]. It is a chronic illness, which in most cases is treated for life; hence the cost associated with it is enormous [17].

Few data exists as regards its cost to the patient and the society in developing countries. These data may help to make a suitable policy in selection of formulations, decision taking and motivation for adherence to the therapy [10, 11].

The study was comprised of 141 patients, out of which, most of the patients (33.3%) were in the age group of 61-70 years. In the study, the male patients (54.6 %) were more predominant in number than the female patients. González-Ortiz M et al performed a study on Efficacy of Glimepiride/Metformin combination versus Glibenclamide/Metformin in patients with uncontrolled type 2 diabetes mellitus [12]. Their findings substantiate the result in our study which also concluded that Metformin/Glimepiride is more effective in reducing HbA1C ($p<0.001$) than other fixed dose combinations.

Among monotherapy, Glipizide ($p < 0.01$) was found to be the most effective anti diabetic drug in reducing HbA1C in our study. It was supported by the study performed by Diana Sherfali et.al which performed the effect of oral Antidiabetic drugs on A1C levels and concluded that Thiazolidinediones and Sulphonylureas are most effective in HbA1C reduction [13]. A meta-analysis of Comparison of different drugs as add-on treatments to Metformin in type 2 diabetes was performed by Monami M et.al which concluded that sulphonylureas are more effective in HbA1C reduction when given as add on to Metformin [14]. These findings are resemblance to our study which shows that Glimepiride as an add to Metformin ($p<0.001$) was the most effective among the add-on-therapy.

In our study, among add-on-therapy, Glimepiride was most cost effective in reducing HbA1C. These findings are similar to those reported by Scott Klarenbach et.al, which performed a prospective analysis on Cost effectiveness of second line anti-hyperglycemic therapy in patients with type-2 diabetes mellitus inadequately controlled on Metformin. They concluded that Sulphonylureas as a second line agent are most cost effective in glycemic control when added to Metformin monotherapy [15].

Considering the HbA1C reduction, the most cost effective drug among fixed dose combinations in our result was Glibenclamide and Metformin. These findings are supported by Christian Diaz de Leon Castaneda et.al which performed Cost effectiveness study of oral hypoglycemic agents in the treatment of outpatients with type-2 diabetes attending a public primary care clinic in Mexico City [16].

The drug interactions were monitored in the prescriptions and there were 12 (5.30%) major interactions. About 71.68% of moderate and 23% minor drug interactions were also present in the study. The interaction between Dalteparin and Clopidogrel was the majorly identified drug interaction (1.42%), in which there will be an enhanced risk of hemorrhage.

About 5 Adverse Drug Reactions were identified in the study, out of which one was Definite and the remaining 4 were Probable. The definite ADR was Furosemide induced Hyponatremia and Vomiting with Naranjo Score of nine.

CONCLUSION: Economic evaluation of therapy should be encouraged to ensure cost effective therapy for diabetic patients. For the initial treatment of Type 2 Diabetes Mellitus, Metformin may be considered as cost-effective monotherapy. If blood glucose is inadequately controlled with monotherapy, Glimepiride may be suggested in terms of cost effectiveness, as an add on to Metformin. For uncontrolled Type 2 Diabetes Mellitus, fixed dose combination of Glimepiride and Metformin can be considered as the best drug of choice with respect to cost effectiveness. Patients who do not obtain optimal glycemic control with a fixed dose combination of oral hypoglycemic agents can be considered with fixed dose triple combinations, out of which combination of Glimepiride, Metformin and Pioglitazone was found to be the best choice.

The use of multiple drugs by patients can contribute to various drug interactions, which may sometimes be severe. This can be prevented by close monitoring of drug therapy and avoiding use of multiple drugs for less severe indications.

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