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Cost minimization analysis of generic and innovator formulations of metformin and its combination with other oral antidiabetic drugs

V. L. Gaekwad¹, V. K. Vadgama^{2*}

¹Department of Pharmacology, Medical College, Baroda, Gujarat, India

²Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat, India

Corresponding Author: Dr. Vishalkumar K. Vadgama

E-mail: dr.vishalvadgama@gmail.com

ABSTRACT

Background

Diabetes mellitus, a chronic condition, requiring lifelong care, affects multiple organs on long term. In India, 8.8% adults suffer from diabetes in 2019 and prevalence is likely to rise up to 11.1% by 2045. Total expenditure behind diabetes varies around 12.6 to 34% in different income groups among rural and urban families. Out of these expenses major portion is spent behind cost of medication. Cost of medicines varies among various company brands and generic products, and hence expenditure on cost of medication can be decreased by proper drug selection. Present study aims at determining cost variability and cost analysis of various antidiabetic formulations available in Indian market.

Materials and methods

Metformin and its combinations with sulfonylureas, pioglitazone and vogliboze were selected for cost analysis in present study. Among sulfonylureas, glibenclamide, gliclazide, glimepiride and glipizide were selected. Cheapest, costliest and median priced formulations were searched for individual drugs and were compared to the price of their generic counterparts.

Results

Innovator formulations for metformin 500mg, 500mg SR, 1000mg SR and combination of metformin 500mg with glipizide 5mg were available at cheaper rate than their generic counterparts. Price of other combinations' cheaper formulations were at least 119.17% to 257.5% higher than generic formulations. Considerable cost variation was observed among different brands, price of costliest preparations are 2.11 to 7.89 times higher than cheapest innovator formulation price.

Conclusion

Innovator formulations of metformin were available at cheaper cost than generic formulations. For combinations of metformin with other antidiabetic drugs, generic were the cheapest one. By prescribing generic antidiabetic formulations or lower cost innovator formulations, one can reduce treatment expenditure by many folds.

Keywords: Cost minimization study, Antidiabetic, Metformin, Generic, Innovator

INTRODUCTION

A chronic metabolic disorder, diabetes is characterized by elevated blood glucose levels. It affects 8.8% of adults in India (20-79 years of age) and this prevalence is expected to rise to 11.3% by 2045. India ranks second among the top ten countries in the 20-79 age groups for the prevalence of diabetes. [1]

Type 2 diabetes mellitus commonly affects adults. It develops when various organs of the body become resistant to the actions of insulin or enough insulin is not secreted. [2] Many factors can lead to development of insulin resistance like genetic abnormalities, lack of physical exercise, obesity, polycystic ovarian syndrome, acromegaly *etc.*[3] Initially increased insulin secretion try to compensate for insulin resistance but over the time, β cells gets exhausted, leading to reduction in β cell mass. This eventually leads to further decline in insulin secretion and uncontrolled hyperglycemia supervenes.[4, 5] Hyperglycemia and glycosylation of various proteins and lipids, and oxidative stress produced by them leads to progressive microvascular and macrovascular damage to various organs manifesting as complications like hypertension, cardiovascular disease, retinopathy, peripheral neuropathy *etc.*[6] In order to minimize these complications, optimum glycemic control by lifelong treatment is must. Patient can achieve these by stringently adhering to antidiabetic treatment, diet plan and life style modifications. But similar to other chronic diseases, nonadherence is common among diabetics. [7, 8] Inadequate knowledge about disease, lack of financial resources, long duration of treatment, expensive medication are prominent among the various reasons of nonadherence to treatment.[8] A study by Ramachandran *et al.* evidently stated that urban - low and middle income groups were spending 34% and 16.9% of their total annual income on diabetes care alone. While expenditure on diabetic care of rural - low and middle income groups was 27% and 12.6%, respectively. [9] These data suggest that Indians are spending considerable amount of their total household income on the treatment of diabetes, which might be one of the important reason behind low compliance.

Cost of medicines varies drastically among various company brands and generic products. If expenditure on cost of medicines is controlled by

selecting proper formulation, one may anticipate improvement in patient's adherence towards antidiabetic treatment. In order to aid this selection, cost analysis of commonly prescribed antidiabetic formulations for type 2 diabetes mellitus available in Indian market was carried out by present study.

MATERIALS AND METHODS

Treatment of type 2 diabetes mellitus is mostly initiated with metformin as monotherapy with suitable doses and is added with other oral antidiabetic drugs as the disease progresses and glucose control worsens. Other common oral antidiabetic agents used are sulfonylureas, pioglitazone and vogliboze. Patients of type 2 diabetes mellitus are often affected by other life style disorders like hypertension, angina pectoris, dyslipidemia *etc.* Hence, as patients are taking more than one type of drugs for their treatment, it becomes difficult for them also to track their treatment regimen, especially for less educated ones. Compliance among them, in general is anticipated to be low, hence it is usually preferred that whenever suitable and available, they are prescribed with fixed dose combinations.

Metformin and its combination with sulfonylureas, pioglitazone and vogliboze were selected for cost analysis in present study. Among sulfonylureas glibenclamide, gliclazide, glimepiride and glipizide were included. [10] Sustained release formulations (SR) were available for metformin and its few combinations which were also included for price comparison.

Prices of generic formulations of selected medicines were obtained from local generic medicine drug dispensing stores of different districts of Gujarat. While prices of innovator formulations of selected medicines were obtained from CIMS and IDR database. [11, 12]

Drugs' prices were analyzed; cheapest, costliest and median priced formulations were searched for above mentioned formulations and were compared to the price of their generic counterparts. Data is presented as absolute numbers as well as percentage cost difference between individual drugs formulations. They were also presented with their cost difference to median priced drug formulation of respective drugs.

Microsoft excel (Version 15.0) was used for data management and calculation. Study assumed that generic drugs and innovative medication are of equal effectiveness and easily available. Only their patient direct cost was taken into account for cost comparison. Present study was carried out at pharmacology departments of government medical college, Bhavnagar, Gujarat and medical college, Baroda, Gujarat, during September, 2019 to November, 2019. Vancouver style has been used for reference citation and listing.

RESULTS

For Metformin, cost of generic 500mg, 500mg SR and 1000mg SR single drug oral formulations were Rs. 5, Rs. 10 and Rs. 11, respectively. Cost of their innovator counterparts varied from Rs. 4.4 to Rs. 20.05 with many formulation nearing price of Rs. 15.73 for 500mg dose, while for 500mg SR dose, cost varied from Rs. 7.43 to Rs. 40 with many falling near price of Rs. 7.43. For 1000mg SR dose, cost varied from Rs. 10 to Rs. 64.5 with many falling near price of Rs. 35.52. These striking findings suggest that cost of cheapest innovator formulations were less even than generic formulations. While innovator medicine were overpriced to their generic counterparts by up to 401%, 400% and 586.36% in case of 500mg, 500mg SR and 1000mg SR, respectively. Even among innovator formulations 500mg, 500mg SR, 1000mg and 1000mg SR dose, price varied from 4.56, 5.38, 3.93 and 6.45 fold between cheapest and costliest formulations. (Table 1, Figure 1)

With metformin and its combination with sulfonylureas, price of generic formulations were less as compared to their innovative counterparts; like cost of generic formulations for metformin 400mgmg+Glibenclamide 5mg was Rs. 11, Metformin 500mg+Gliclazide 80mg was Rs. 24, Metformin 500mg+Glimepiride 1mg was Rs. 15, and Metformin 500mg+Glimepiride 2mg was Rs. 14.66;

while their cheapest innovator counterparts were selling at the price of Rs. 15, 28.6, 22.9 and 29.9, respectively and their costliest counterparts were selling at staggering high prices, for Rs. 43, 106.66, 97 and 235.96, respectively. Although, few innovator formulations of metformin 500mg+ glipizide 5mg were cheaper than its generic counterpart, its median cost of innovator formulation was up to 30.64% higher than generic formulation. Considerable price difference was found in between prices of cheapest innovator and costliest innovator formulations. The most expensive formulations for metformin 400mgmg+Glibenclamide 2.5 mg and 5mg, Metformin 500mg+Gliclazide 80mg, Metformin 500mg+Glimepiride 1mg and 2mg also their SR preparations, Metformin 1000mg+Glimepiride 1 and 2mg SR and Metformin 500mg+ Glipizide 5mg were 2.87, 2.87, 3.73, 4.23, 7.89, 2.11, 2.76, 4.11, 4.7 and 7.44 fold costlier than their respective cheapest innovator formulations. (Table 1, Figure 1)

While for metformin and its combinations with pioglitazone and vogliboze, price of generic formulations were less as compared to their innovative counterparts; like cost of generic formulations was for Metformin 500mg+Pioglitazone 15mg was Rs. 20, Metformin 500mg+Vogliboze 0.2mg SR was Rs. 12, Metformin 500mg+Vogliboze 0.3mg was Rs. 14,; while their cheapest innovator counterparts were selling at the price difference of 164.25%, 257.5% and 234.64%, respectively; and their costliest counterparts were selling at staggering high prices, for Rs. 77, 100 and Rs. 97, respectively. Considerable price difference was found in between prices of cheapest innovator and costliest innovator formulations. The most expensive formulations for Metformin 500mg+Pioglitazone 15mg, Metformin 500mg+Vogliboze 0.2mg SR and Metformin 500mg+Vogliboze 0.3mg were 2.34, 3.24 and 2.95 fold costlier than their respective cheapest innovator formulations. (Table 1, Figure 1)

Table 1– Table showing price variability of metformin and its combinations with various oral antidiabetic drugs & their individual comparison with their generic counter parts. (Cost in Rs. per 10 formulations)

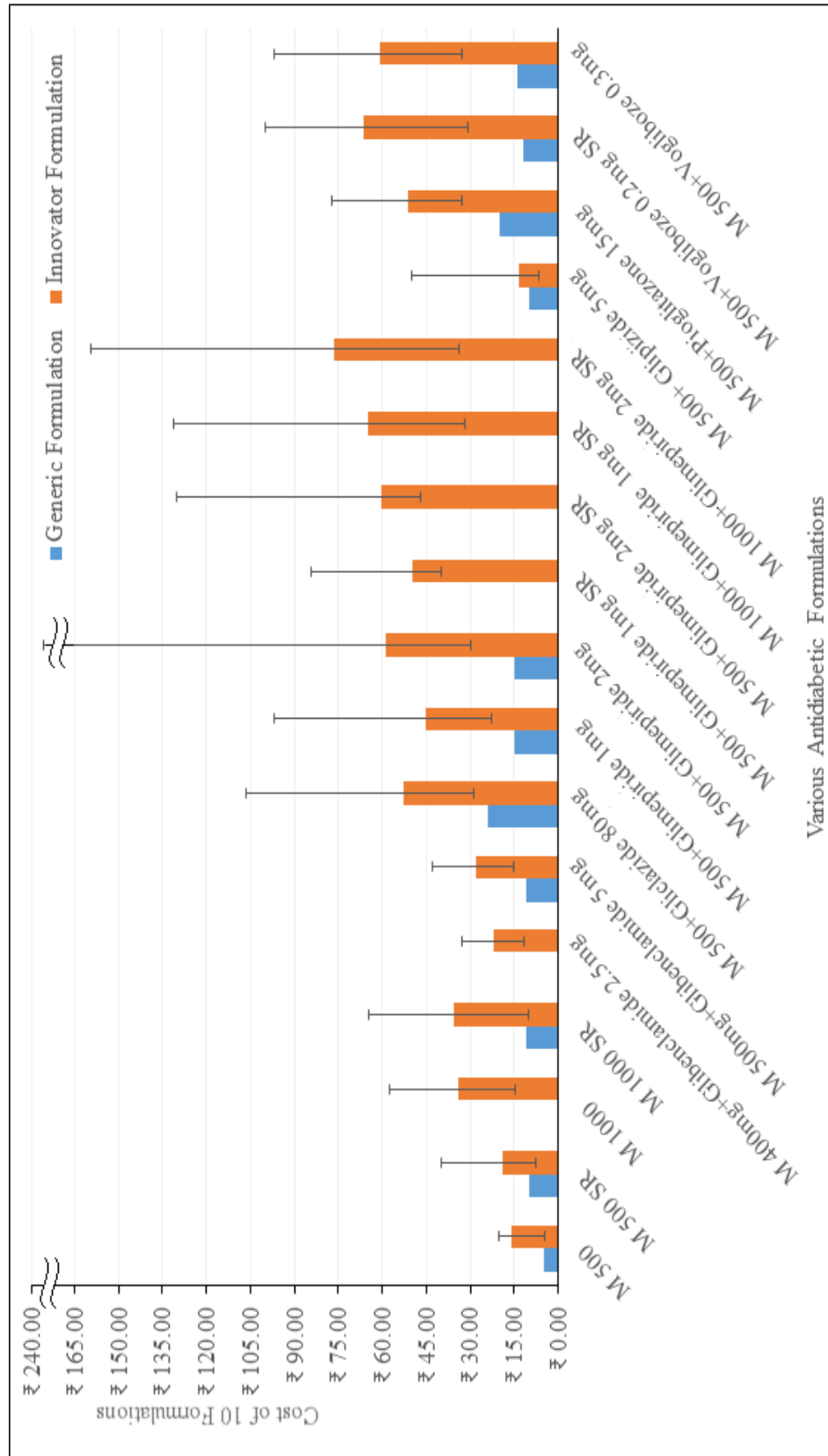
Drug and Dosage of Formulations	Cost of Generic Formu.	Cheapest Innovator Formulation	Median Innovator Formulation	Costliest Innovator Formulation	Fold Increase in Cost \$
Metformin 500mg	5	4.4 (88%)*	15.73	20.05 (401%)*	4.56
Metformin 500mg SR	10	7.43 (74.3%)*	18.92	40 (400%)*	5.38
Metformin 1000mg	N.A.	14.6	34.2	57.46	3.93
Metformin 1000mg SR	11	10 (90.91%)*	35.525	64.5 (586.36%)*	6.45
Metformin 400mg+ Glibenclamide 2.5mg	N.A.	11.5	22	33	2.87
Metformin 500mg+ Glibenclamide 5mg	11	15 (136.36%)*	28	43 (390.9%)*	2.87
Metformin 500mg+ Gliclazide 80mg	24	28.6 (119.17%)*	52.5	106.66 (444.42%)*	3.73
Metformin 500mg+ Glimepiride 1mg	15	22.9 (152.67%)*	44.95	97 (646.67%)*	4.23
Metformin 500mg+ Glimepiride 2mg	14.66	29.9 (203.96%)*	59	235.96 (1609.55%)*	7.89
Metformin 500mg+ Glimepiride 1mg SR	N.A.	40	49.55	84.28	2.11
Metformin 500mg+ Glimepiride 2mg SR	N.A.	47	60.5	130	2.76
Metformin 1000mg+ Glimepiride 1mg SR	N.A.	31.9	65	131	4.11
Metformin 1000mg+ Glimepiride 2mg SR	N.A.	33.9	76.5	159.5	4.7
Metformin 500mg+ Glipizide 5mg	10	6.72 (67.2%)*	13.64	50 (500%)*	7.44
Metformin 500mg+ Pioglitazone 15mg	20	32.85 (164.25%)*	51.335	77 (385%)*	2.34
Metformin 500mg+ Vogliboze 0.2mg SR	12	30.9 (257.5%)*	66.5	100 (833.33%)*	3.24
Metformin 500mg+ Vogliboze 0.3mg	14	32.85 (234.64%)*	60.95	97 (692.86%)*	2.95

\$ = Fold increase in cost between cheapest to costliest innovator formulations.
(text)* = price difference (in percentage) between individual innovator formulation to its generic counterpart.

N.A. = Generic formulation information not available.

SR= sustained release formulations

Figure 1– Figure showing price variability of metformin and its combinations with various oral antidiabetic drugs & their individual comparison with their generic counter parts. (Cost in Rs. per 10



Various Antidiabetic Formulations

Note - Height of individual bar represents median cost of formulation in Rs. per 10 formulations and error bars represent range of cheapest and costliest formulation's cost in Rs. per 10 formulations.

DISCUSSION

Diabetes is a chronic life style disorder, requiring lifelong therapy. Newly diagnosed diabetic patients with low levels of hyperglycemia are started with life style modifications, weight reduction and many a times metformin monotherapy. As disease progresses, effect of even full doses of metformin becomes insufficient to maintain blood glucose within normal range. Hence, metformin has to be supplemented with other oral antidiabetic drugs like sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors or others in order to maintain blood glucose within normal range.

As, an Indian study reported, multiple drug therapy in case of diabetes and resultant high drug cost often lead to non-adherence to the therapy. [8] Up to 96.19% of analyzed patients perceived that cost of medicines were high or they were not having enough financial resources to cope with expenditures of drug therapy. [8] Hence, in order to improve compliance to the treatment of diabetes, one has to simplify drug administration whenever possible and also reduce cost of therapy. Both of these targets can be achieved by prescribing cost effective fixed drug combinations whenever they are rational and feasible.

With present study, we analyzed cost of generic and innovator formulations of metformin and its combinations with other commonly used antidiabetic drugs. It was a surprising finding that few innovator formulations of metformin were cheaper even than their generic counterparts. Though, few innovator formulations were sold at 400% to 586.36% higher cost than their generic counterparts. Also, price varied greatly in between innovator formulations, and with selection of cheaper formulation, one can decrease cost of therapy up to 5.38 to 6.45 fold.

Whenever available, generic formulations of metformin and various sulfonylureas were cheaper than their innovator counterparts. Considerable cost

difference was found between cost of metformin 500mg and glimepiride 1mg and 2mg combinations; innovator formulations were at least 152.67% and 203.96% costlier, respectively. Few innovator formulations of these combinations were even sold at staggering overprice of 646.67% and 1609.55% for 1mg and 2mg combinations respectively, than their generic counterparts. Even if one opts for innovator formulation, one may select cheapest innovator formulation of metformin 500mg and glimepiride 1mg or 2mg combinations and can decrease cost of drug therapy up to 7.89 and 7.44 folds, respectively.

Generic formulations of combination of metformin 500mg and pioglitazone 15mg were up to 64.25% to 385% cheaper than their innovator counterpart. While cheapest innovator formulations of combination of metformin 500mg with voglibose 0.2mg SR as well as with voglibose 0.3mg were at least 257.5% and 234.64% costlier than their generic counterparts. Cost increased considerably in case of their costliest formulations, being overpriced at 833.33% and 692.86%, respectively.

Selection between generic formulations and innovative formulations is a sole personal preference. Due to various personal factors and pre-occupations, even if one prefers innovative formulations, one may select the cheapest innovator formulation and can save substantially, towards cost of antidiabetic drug therapy.

CONCLUSION

For selected antidiabetic drugs, the prices of generic formulations are found to be lower than all of their innovative counterpart formulations except metformin single drug formulations. With combination of metformin and other oral antidiabetic drugs, the cost of innovative formulations varied many folds.

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