J. Pharm. Res. 2024;23(2):77–82

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

ORIGINAL ARTICLE

Cost Analysis of DPP4 and SGLT2 Inhibitors - "Dilemma of the Prescribing Physician - Which Brand to Choose?"

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ARTICLE INFO

Article history:
Received 09-03-2024
Accepted 14-05-2024
Published 06.08.2024

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https://doi.org/10.18579/jopcr/v23.2.15

ABSTRACT

Diabetes mellitus (DM) is a complex and heterogeneous group of chronic metabolic diseases causing dreaded complications increasing human sufferings, and a costly disease to manage in low/middle-income countries, which is burdensome for the most vulnerable populations, cause financial strain on individuals and family members. The purpose of the study was to analyze the price variability of different brands of sodium glucose co-transporter 2 inhibitors (SGLT2i) and dipeptidyl peptidase 4 inhibitors (DPP4i) and their combinations. The present study was an observational analytical one. The highest and lowest price of each SGLT2i and DPP4i in the same strength marketed by different pharmaceutical companies, were collected from Current Index of Medical Specialties (Jan–April 2023), Indian Drug Review (IDR 2023), Drug Today (April – July 2023) drug manuals. Calculations were done in Indian Rupees per 10 tablets/capsules. For each drug, the cost ratio and percentage of price variation (PPV) were calculated. Among DPP4i, sitagliptin 50 mg has a maximum cost ratio (5.30) and PPV (1083.66%), while sexagliptin 2.5 mg has minimal cost ratio (1.55) and PPV (55.08%). Among SGLT2i, dapagliflozin 5 mg had the highest cost ratio (10.79) and PPV (978.79%) and remogliflozin100 mg had the lowest cost ratio (1.57) and PPV (56.94%) and among combinations dapagliflozin 10 mg+ metformin 500 mg has the highest cost ratio (6.66) and PPV (565.75%), while empagliflozin 12.5 mg + metformin 500 mg has the lowest cost ratio (1.04) and PPV (4.00%). Current study shows large differences in cost ratio as well as PPV between brands. To reduce the financial burden and treatment adherence, physicians must prescribe less expensive drugs.

Keywords: Cost analysis; Cost ratio; Percentage of price variation; Diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a complex and heterogeneous group of chronic metabolic diseases characterized by elevated levels of blood glucose and triggers a series of vascular events that affects kidney, vision loss, ischemic heart disease, strokes, and peripheral artery occlusive diseases causing dreaded complications and increase in human sufferings [1,2]. Patients with uncontrolled DM are at the risk of developing acute metabolic complications and chronic microvascular and macrovascular complications that affects patients' survival and quality of life [3]. Over 90% of DM cases are Type 2 (T2DM), a condition characterized by deficient insulin secretion by pancreatic islet β-cells, tissue insulin resistance (IR) and an inadequate compensatory insulin secretory response [4]. This chronic non-communicable disease has high morbidity and mortality and at present times a serious public health problem worldwide [2]. Current global estimates suggest that 537 million adults (aged 20-79 years) are affected by the disease and one in ten have diabetes. This number is expected to increase to 643 million by 2030 and 783 million by 2045 [5]. In India, approximately 77 million people over the age of 18 have T2DM and almost 25 million are at a higher risk of developing diabetes in the near future [6]. Intensive pharmacotherapy improves delays or prevents the progression of chronic complications of DM [7]. DM is a costly disease to manage in low/middle-income countries, which is burdensome for the most vulnerable populations, cause financial strain on individuals and health systems [8], particularly when associated with other comorbidities.

Many oral hypoglycaemic agents (OHA) are used for the treatment of diabetes with a specific mechanism of action but differ in their pharmacokinetic properties,

including the duration of action and/or excretion and metabolism[9]. Current OHA for T2DM are aimed at suppressing hepatic glucose output, stimulating insulin release, mitigating glucose absorption, and increasing peripheral glucose utilization. These agents including biguanides, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, and thiazolidinediones are often associated with significant adverse reactions[10]. The dipeptidyl peptidase 4 inhibitors (DPP4i) sitagliptin, saxagliptin, vildagliptin and linagliptin were introduced after 2006[11]. Apart from antihyperglycemic effects, DPP4i possesses antihypertensive effects, anti-inflammatory effects, antiapoptotic effects, and immunomodulatory effects on the heart, kidneys, and blood vessels independent of the incretin pathway[12]. Sodium–glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 (GLP-1) receptor agonists decrease the risks of major adverse cardiovascular events, hospitalization rate for heart failure, and progression of diabetic kidney disease, irrespective of diabetes status. Hence, SGLT2i are called disease-modifying therapy for chronic kidney disease, primary kidney disease, or altered kidney function[7,13]. Four SGLT2i, (canagliflozin, dapagliflozin, empagliflozin, and remogliflozin) are approved by Food Drug Administration (FDA) for their use in adults[14].

These agents targeted to control DM and alleviate the symptoms associated with it, as well as the long-term complications. In addition, these agents can help clinicians in initiating individualized therapies for diabetic patients considering different elements such as efficacy, side effects, costs, comorbidities, weight gain and blood glucose levels[9]. Study suggests that SGLT2i and DPP4i Fixed Dose Combinations (FDC) is a suitable option for Indian T2DM as they are safer, rapidly acting and sustained glycemic control. They also improve both insulin resistance and beta cell function, reduce body weight as well as blood pressure (extraglycemic benefits). They are overall cost effective and reduces pill burden (adherence and compliance improves) of the patients[15]. SGLT2i and DPP4i are available in various strengths in combinations with wide variation in prices, which makes it difficult for physicians to choose the least expensive prescription for their patients. The increased cost variations of these medications lead to poor treatment compliance and, as a result, lower quality of life, increasing the financial burden on patients as well as family members. The knowledge of cost variations among various brands of SGLT2i and DPP4i may be used to develop a more cost-effective treatment regimen to increase patient compliance and reduce the risk of therapy failure.

There are numerous literature[16–20] on cost-effective analysis of DPP4i and SGLT2i. However, few literature[21–25] have been found to demonstrate the cost analysis of other antidiabetic drugs. To the best of our knowledge, no studies have been performed yet on cost analysis of different brands of DPP4i and SGLT2i marketed in India. This research aims to look at the cost differences of SGLT2i and DPP4i with their combinations, between different brands that are presently available in the Indian pharmaceutical market.

MATERIALS AND METHODS

This analytical study was conducted in the Department of Pharmacology at Assam Medical College and Hospital during the July- September 2023. "Current Index of Medical Specialities" (CIMS Jan–April 2023 44th year), "Indian Drug Review" (IDR 2023, 29th year, Vol- XXIX; Issue 3), Drug Today (April – July 2023) drug manuals, https://www.netmeds.com and https://www.1mg.com were used to analyze the variation in prices of different DPP4i and SGLT2i brands available in India. The National Pharmaceutical Pricing Authority (NPPA) website was used to gather information about the generic drug pricing set by the NPPA under the Drug price control order (DPCO). The cost of a particular drug (single drug or drug combinations) in the same strength and number of brands being manufactured by different companies was compared in Indian rupees per 10 tablets/capsules. The drugs manufactured by only one company or by different companies, however, in different strengths were excluded. Parenteral formulations were also excluded. The following formulas[21,24], were used to calculate the Cost ratio and Percentage of Price Variation (PPV).

$$Cost\ ratio = \frac{Highest\ cost}{Lowest\ cost}$$

$$PPV = \frac{Price\ of\ the\ most\ expensive\ brand - Price\ of\ the\ least\ expensive\ brand}{Price\ of\ the\ least\ expensive\ brand} \times 100$$

Statistical Analysis: The data were compiled in tables and results expressed in numbers and percentages.

RESULTS

Total 35 drugs (15 individual preparations and 20 combined preparations), were available in 420 different strengths, manufactured by different pharmaceutical companies were analyzed. Table 1 shows the cost ratio and PPV for DPP4i. In this group, sitagliptin 50 mg has a maximum cost ratio (5.30) and PPV (1083.66%), while sexagliptin 2.5 mg has minimal cost ratio (1.55) and PPV (55.08%).

Table 2 shows the PPV and cost ratio of SGLT2i. Within these groups, dapagliflozin 5 mg had the highest cost ratio (10.79) and PPV (978.79%) and remogliflozin100 mg had the lowest cost ratio (1.57) and PPV (56.94%).

Table 3 shows the PPV and cost ratio of combined formulations. A total 20 combined preparations wereanalyzed. Here, dapagliflozin 10 mg+ metformin 500 mg has the highest cost ratio (6.66) and PPV (565.75%), while empagliflozin12.5 mg +metformin 500 mg has the lowest

Table 1: Price variation in DPP4i

Drug and Doses (mg)	No. of brands	Maximum price (Rs)	Minimum price (Rs)	Cost ratio	Percentage of Price Variation (%)
Sitagliptin 25 mg	5	371.00	70.00	5.30	430.00
Sitagliptin 50 mg	18	378.57	35.00	11.84	1083.66
Sitagliptin 100 mg	61	449.47	65.00	6.91	591.49
Sexagliptin 2.5 mg	4	432.00	278.57	1.55	55.08
Sexagliptin 5 mg	6	590.00	308.00	1.92	91.56
Vildagliptin 50 mg	19	220.00	29.00	7.59	658.62
Vildagliptin 100 mg	20	380.00	60.00	6.33	533.33
Linagliptin 5 mg	9	309.00	95.00	3.25	225.26
Teneligliptin 20 mg	25	217.50	55.00	3.96	295.46

Table 2: Price variation in SGLT2i

Drug and Doses (mg)	No. of brands	Maximum price (Rs)	Minimum price (Rs)	Cost ratio	Percentage of Price Variation (%)
Dapagliflozin 5 mg	18	312.85	29.00	10.79	978.79
Dapagliflozin 10 mg	24	330.00	44.00	7.50	650.00
Empagliflozin 10 mg	4	534.00	150.00	3.56	256.00
Empagliflozin 25 mg	5	647.00	189.00	3.42	242.00
Canagliflozin 100 mg	4	1450.00	590.00	2.46	145.76
Remogliflozin 100 mg	6	215.00	137.00	1.57	56.94

Table 3: Price variation in Combinations

Drug and Doses (mg)	No. of brands	Maximum price (Rs)	Minimum price (Rs)	Cost ratio	Percentage of Price Variation (%)
Sitagliptin 50 mg + Metformin 500 mg	17	230.00	59.33	3.88	287.66
Sitagliptin 50 mg + Metformin 1000 mg	15	231.67	92.00	2.52	151.82
Sitagliptin 100 mg + Metformin 1000 mg	13	412.86	139.00	2.97	197.02
Sexagliptin 5 mg + Metformin 500 mg	2	560.00	468.57	1.20	19.52
Sexagliptin 5 mg + Metformin 1000 mg	5	557.15	321.43	1.73	73.34
Sexagliptin 5 mg + Dapagliflozin 10 mg	2	1560.00	890.00	1.75	75.28
Teneligliptin 20 mg + Metformin 500 mg	23	162.50	79.00	2.06	105.70
Teneligliptin 20 mg + Metformin 1000 mg	15	186.00	89.80	2.07	107.13
Dapagliflozin 5 mg + Metformin 500 mg	15	178.00	70.00	2.54	154.29
Dapagliflozin 10 mg + Metformin 500 mg	10	685.72	103.00	6.66	565.75
Dapagliflozin 10 mg + Metformin 1000 mg	17	721.00	130.00	5.54	454.62
Dapagliflozin 10 mg + Sitagliptin 100 mg	13	220.00	180.00	1.23	22.23
Dapagliflozin 10 mg + Vildagliptin 100 mg	15	200.00	142.00	1.41	40.85
Empagliflozin 12.5 mg + Metformin 500 mg	3	416.00	400.00	1.04	4.00
Empagliflozin 12.5 mg + Metformin 1000 mg	3	437.00	420.00	1.04	4.05
Empagliflozin 25 mg + Linagliptin 5 mg	4	861.00	820.00	1.05	5.00
Empagliflozin 10 mg + Linagliptin 2.5 mg	4	788.00	750.00	1.05	5.06
Remogliflozin 100 mg + Metformin 500 mg	5	159.00	128.00	1.24	24.22
Remogliflozin 100 mg + Metformin 1000 mg	6	175.00	144.00	1.22	21.53
Remogliflozin 100 mg + Vildagliptin 50 mg	5	163.90	140.00	1.17	17.07

cost ratio (1.04) and PPV (4.00%). Figure 1 shows the PPV of DPP4i and SGLT2i.

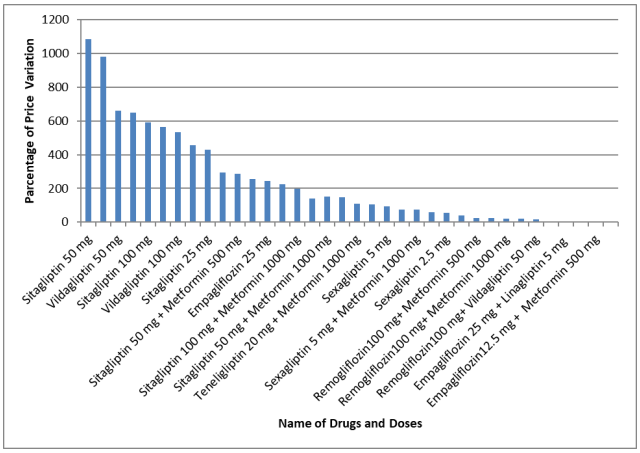

Fig. 1: PV of DPP4i and SGLT2i and Combination

DISCUSSION

In this study, SGLT2i, DPP4i and their Fixed Dose Combinations (FDCs) were analyzed. Most of the drugs have PPV above 100%, which is not favorable. The findings of the present study suggest that there are large PPV among DPP4i and SGLT2i and their FDCs. Among DPP4i, it was observed that maximum PPV was seen in sitagliptin 50 mg (1083.66%) followed by vildagliptin 50 mg (658.62%), sitagliptin 100 mg (591.49%), vildagliptin 100 mg (533.33%), sitagliptin 25 mg (430.00%), teneligliptin 20 mg (295.46%), linagliptin 5 mg (225.26%). Among SGLT2i, highest PPV was seen in dapagliflozin 5 mg (978.79%) followed by dapagliflozin 10 mg (650.00%), empagliflozin 10 mg (256.00%), empagliflozin 25 mg (242.00) and canagliflozin 100 mg (145.76%). In 2018, Mehani R et al., has also reported low PPV of teneliglipin 20 mg 231 % [24].

In combination therapy, it was observed that maximum PPV was seen in dapagliflozin 10 mg+ metformin 500 mg (565.75%) followed by dapagliflozin 10 mg + metformin 1000 mg (454.62%), sitagliptin 50 mg + metformin 500 mg (287.66%), sitagliptin 100 mg + metformin 1000 mg (197.02%), sitagliptin 50 mg + metformin 1000 mg (151.82%), dapagliflozin 5 mg + metformin 500 mg (154.29%) teneligliptin 20 mg + metformin 1000 mg (107.13%) and teneligliptin 20 mg + metformin 500 mg (105.70%). However, in 2020 Shyam S et al. and in 2022 Amaravati RVC et al, has reported lower PPV of teneliglipin 20 mg + metformin 500mg combination 63% and 79% respectively (21,23). Though the market price of all available brands of empagliflozin12.5 mg + metformin 500 mg combination was very high, their PPV (4.00%) and cost ratio (1.04) was very low in this study.

A cost-effectiveness study from Brazil demonstrated that, the combination therapy metformin + sitagliptin compared to metformin + glibenclamide was shown not to be cost-effective[18]. On the other hand, a cost-utility analysis of saxagliptin + dapagliflozin versus gliclazide + insulin glargine shows, saxagliptin + dapagliflozin combination was considered a cost-effective oral hypoglycemic therapy[3]. Sequential addition of SGLT2i to DPP4i may be considered cost-effective compared with traditional treatment who fails to achieve glycemic goal on metformin[20].

DPP4i + SGLT2i combination in the management of Asian Indian patients with T2DM, where phenotype is characterized by increased visceral adiposity, lower metabolic tolerance, and increased cardio-renal risk may be relevant in this regard[23]. There is an increasing prevalence of diabetic kidney disease (DKD) and ultimately develops end stage kidney disease (ESKD)[26]. Several studies demonstrate the benefits of SGLT2i on CKD progression and ESKD and better CV outcome[26–30]. Remogliflozin, lately introduce SGLT2i, relatively affordable and more than 50% cheaper than the existing drugs of the same class. However, long term safety and efficacy data especially on cardiovascular and renal outcomes are currently lacking this drug[31]. The safety of DPP4i has been demonstrated in several trials in patients with different degrees of renal impairment. DPP4i may improve microvascular structure and function, reducing the burden of microangiopathy may translate into improved CV outcomes in DM[32]. Safety, efficacy, and bioavailability of newly approved FDC drugs used in T2 DM such as SGLT2i suggests that currently they would be the better treatment option[33]. Another beneficial effect of sitagliptin is that it can be used as prophylaxis of acute Graft-versus-Host disease in combination with tacrolimus plus sirolimus[34]. Saxagliptin improves glycemic control, reduced the development and progression of microalbuminuria[35], linagliptin and sitagliptin is used among adults with T2DM and with high CV and renal risk as add on[36,37]. The benefits of DPP4i and SGLT2i have been demonstrated in various clinical trials, and they are now recommended by expert organizations as add-on therapy in T2DM patients with known CV or renal conditions, or at high risk of developing these conditions. They not only improve diabetes outcomes, but also improve CV and renal outcomes[26–37]. These newer antidiabetic drugs appear to be cost-effective therapy as second line options with T2DM compared to classic antidiabetic drugs[38]. When SGLT2i are introduced in the first two years of diagnosis, it was suggested that these drugs attenuate the phenomenon of legacy effect. An early treatment with these drugs might thus promote a long-lasting benefit to the patients[39]. Presently in India, empagliflozin and linagliptin combination is a crucial component in the management of T2DM with cardio- renal co-morbidities[40]. But the limitation of using these drugs is mainly the cost. If these groups of drugs included in DPCO

and fixed the price for all available brands, then it will be beneficial to general population.

Strengths and Limitations: Strength of our study is sources of information obtained from various drug manuals and websites where all currently available drug prices were listed. Limitation is that, only DPP4i and SGLT2i were included in this study. Other conventional oral anti diabetic drugs, insulin preparations and other injectable were not included in the study.

CONCLUSION

Diabetes is a common disease and requires lifelong therapy. The cost of drugs plays an important role in patient care and treatment adherence. High price variation of same drug of same strengths should not be encouraged. All physicians need to keep themselves updated with the latest prices and price variation of different brands. Pharmacoeconomic awareness among undergraduate MBBS students as well as new prescribers about wide variation in prices of same drugs will plays major role in their future practice. Availability of manual of comparative drug prices and implementation of price control policies should be encouraged to reduce the cost of treatment and promote rationale use of drugs and increase patient compliance to treatment. Stakeholders should frame policies like "one drug one price" and include more new drugs in essential drug list under DPCO to ensure cost effective therapy, instead of obliging for generic drugs to reduce cost of therapy.

Acknowledgement

- **Source of support :** Nil.
- **Conflict of interest:** None declared.
- **Ethical approval :** Not required. As source of data collected does not involve any human data hence this study does not require Institutional Ethics Committee approval.
- **Contribution Details**
  - **Conception and design:** Hiteswar Saikia, Anju L. Saikia
  - **Acquisition of data, Literature search:** Hiteswar Saikia, Anju L. Saikia
  - **Analysis and interpretation of data:** Hiteswar Saikia, Prabhat Ranjan Baruah, Anju L. Saikia
  - **Manuscript preparation, editing and review:** Hiteswar Saikia, Anju L. Saikia, Prabhat Ranjan Baruah

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