Cost Variation Analysis of Metformin-Based Dual Fixed-Dose Combinations Prescribed in India

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Received:2025-02-19, Revised: 2025-08-30, Accepted: 2025-09-09, Published:2025-09-30

Abstract

Background: Metformin is the initial pharmacological intervention for managing type 2 diabetes mellitus (T2DM). However, its effectiveness for achieving optimal glycemic control diminishes over time, requiring the addition of other oral antidiabetic drugs (OADs) to the treatment regimen. The widespread adoption of metformin-based fixed-dose combinations (FDCs) in India necessitates an investigation into their impact on affordability and access. This study, therefore, undertook a cost variation analysis of available dual FDCs containing 500 mg of metformin to illuminate these implications.

Methods: The cost data were sourced from retail websites. We analyzed cost variation by calculating the cost variation percentage (CV%) and the average cost of all FDCs. The relationship among cost variation, average cost, and the number of manufacturing companies was statistically assessed using Pearson's correlation in Microsoft Excel.

Results: Among the 15 FDCs analyzed, the metformin + dapagliflozin combination exhibited the most substantial cost variation, reaching 436.2%. Conversely, the metformin + saxagliptin combination recorded the highest average cost per tablet, at 45.16 rupees (equivalent to 0.52$). A statistically significant negative Pearson's correlation was observed between the average cost of drugs and the number of manufacturing companies across all FDCs ($r = -0.595$, $p = 0.019$*) and in the metformin + dipeptidyl peptidase-4 inhibitors (DPP4is) group ($r = -0.900$, $p = 0.037$*).

Conclusion: OIn our study, the co-administration of metformin with the newer therapeutic agents (dapagliflozin and saxagliptin) demonstrated the highest variability in pharmaceutical pricing. This finding underscores the necessity for regulatory intervention regarding the costs of these FDCs within the Indian market.

J Pharm Care 2025; 13(3): 217-223.

Keywords: Cost Variation Analysis; Metformin; Fixed-Dose Combinations

Introduction

Type 2 diabetes mellitus (T2DM) is a cluster of conditions marked by hyperglycemia, disruptions in the metabolism of fats, carbohydrates, and proteins, and an elevated risk of both microvascular and macrovascular complications. This disease poses a considerable threat and has reached epidemic levels in both developed and developing nations. It is projected that by 2045, the global prevalence of type 1 DM (T1DM) or T2DM among adults will reach an estimated 784 million individuals. (1) Currently, India faces a significant public health challenge, with approximately 77 million adults over the age of 18 diagnosed with T2DM and an additional 25 million individuals classified as prediabetic. Furthermore, the annual healthcare expenditures associated with diabetes in India are anticipated to exceed 1,260 billion by 2025. (2)

T2DM is typically managed through a progressive intervention strategy. This approach initiates with lifestyle modifications, followed by the administration

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of oral hypoglycemic agents. Insulin therapy, either as a monotherapy or in conjunction with oral medications, is reserved as a final measure to achieve optimal glycemic control. (3,4,5)

Metformin is widely recognized as the preferred initial monotherapy for managing T2DM. (6,7) However, its long-term effectiveness in maintaining glycemic control can be limited, often requiring the subsequent integration of additional therapies.

Combination therapies constitute approximately 40% of available antidiabetic medications. These therapies are crucial for attaining glycemic control in T2DM management, as they offer enhanced efficacy, tolerability, and patient compliance by targeting multiple pathways through diverse mechanisms. (8) Analysis of prescription patterns indicates that over 90% of individuals with T2DM necessitate combination therapy (9), and approximately two-thirds of these patients receive dual therapy, with metformin serving as a foundational component. (10)

Various pharmaceutical companies produce fixed-dose combinations (FDCs) that pair metformin with a range of other oral antidiabetic drugs (OADs), including sodium-glucose co-transporter-2 inhibitors (SGLT-2is), dipeptidyl peptidase-4 inhibitors (DPP4is), thiazolidinediones (TZDs), sulfonylureas (SUs), meglitinide analogues, and alpha-glucosidase inhibitors (α-Gis).

The chronic nature of T2DM necessitates the continuous administration of metformin-based FDCs to achieve the desired euglycemia. This lifelong treatment significantly contributes to the escalating costs of diabetes management. Notably, in India, these FDCs are frequently prescribed to newly diagnosed T2DM patients due to several advantages, including a reduced pill burden, affordability, and improved patient adherence. Despite the prevalence of numerous irrational FDCs available in India without the necessary approval from the Central Drugs Standard Control Organization (CDSCO), a study by McGettigan P. et al. indicated that 20 out of 25 commercially available metformin-based FDCs were approved in India. (11) Nevertheless, 23 irrational metformin-based FDCs were banned in 2018 (10), even though these combinations represent approximately 67% of all diabetes medication sales. In India, five top-selling metformin + sulfonylureas FDCs collectively represent 500 marketed brands. (12) Additionally, FDCs combining metformin with SGLT-2is and DPP4is received approval in India in 2015. These newer combinations offer the added benefits of cardioprotective and renoprotective effects. However, replacing sulfonylureas and other oral medications with these newer drug classes within FDCs leads to a significant increase in treatment costs. (13)

Academic literature shows a gap in research regarding the cost variations of metformin-based FDCs within India. Given the high prevalence of diabetes and the extensive use of these metformin-based FDCs across the country, it is critical to analyze the cost variations among different available combinations of metformin 500 mg with other OADs.

Methods

This study aims to investigate the cost variations across different brands of FDCs containing metformin 500 mg with various OADs, such as DPP4is, SGLT2is, SUs, TZDs, meglitinides, and α-Gis. The cost data and the number of manufacturers for these FDCs were sourced from prominent retail websites-1mg.com and Netmeds. These platforms are widely utilized by Indian consumers for online medicine purchases. FDCs containing TZDs were excluded from this analysis due to the limited number of manufacturers, with only one company producing combinations of metformin with pioglitazone and rosiglitazone. Subsequently, cost analysis for the remaining FDCs within each group was conducted by determining the cost variation percentage (CV%) and average cost.

Cost variation was calculated as follows:

Cost variation% = Maximum cost - Minimum cost: Minimum cost x 100 (7)

Descriptive data, presented as percentages, were tabulated and graphically displayed. To assess the relationship among cost variation, average cost, and the number of manufacturing companies, Pearson's correlation test was employed using Microsoft Excel. This statistical tool is well-suited for evaluating the strength and direction of linear relationships between two continuous variables. A p-value of < 0.05 was established as the threshold for statistical significance.

Ethical Approval

This study, being an analytical cost analysis, was exempt from Institutional Academic Ethics Committee approval.

Consequently, the requirement for written informed consent for participation was waived, with no use of patient data for research or educational purposes. All procedures adhered to the guidelines stipulated in the Declaration of Helsinki.

Results

Cost Variation Analysis

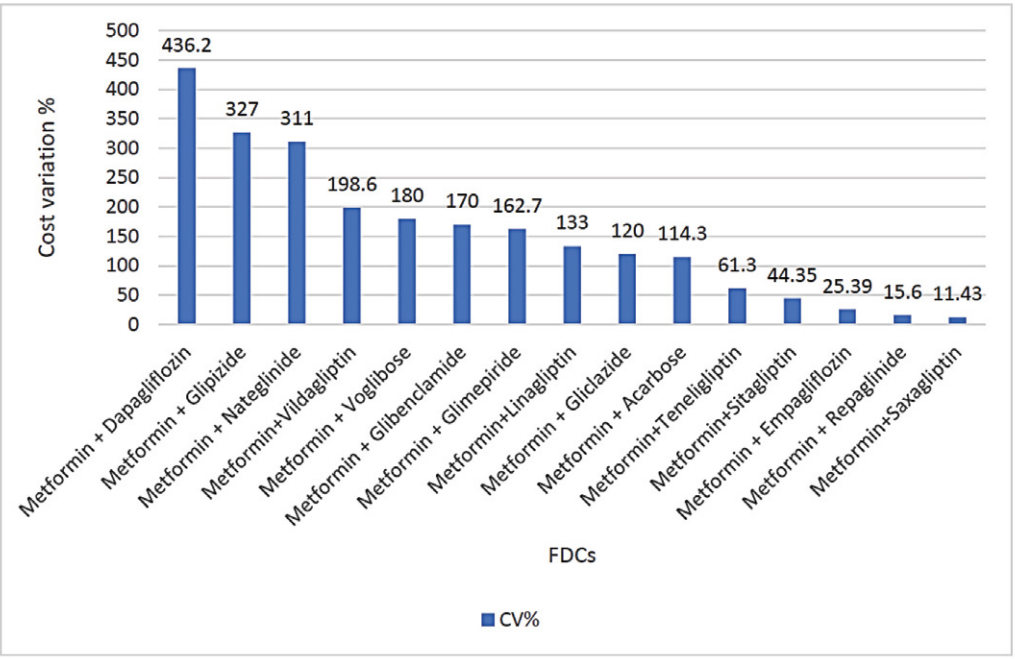
Fifteen FDCs of metformin 500 mg with five different OADs—DPP4is, SGLT2is, SUs, meglitinides, and α-Gis—were analyzed to determine their average cost and CV% using the formula mentioned above (Table 1).

Table 1. Cost analysis of Metformin FDC

No.	Drug combinations	Dose	Cost variation (%)	Average cost	No. of companies
Metformin+DPP4 inhibitors					
1	**Metformin+Vildagliptin**	500mg+50 mg	198.6	12.75 ₹ (0.15 $)	11
2	**Metformin+Sitagliptin**	500mg+100 mg	44.35	15.22 ₹ (0.17 $)	10
3	**Metformin+Teneligliptin**	500mg+20 mg	61.3	15.8 ₹ (0.18 $)	11
4	**Metformin+Saxagliptin**	500mg+5 mg	11.43	45.16 ₹ (0.52 $)	3
5	**Metformin+Linagliptin**	500mg+2.5 mg	133	11.9 ₹ (0.14 $)	8
Metformin+SGLT2 inhibitors					
1	**Metformin + Dapagliflozin**	500mg+10 mg	436.2	18.6 ₹ (0.28 $)	14
2	**Metformin + Empagliflozin**	500mg+12.5 mg	25.39	36.7 ₹ (0.42 $)	3
	Metformin + Sulfonylureas				
1	**Metformin + Glimepiride**	500mg+ 1 mg	162.7	8.76 ₹ (0.10 $)	15
2	**Metformin + Glipizide**	500mg+ 5 mg	327	2 ₹ (0.02 $)	9
3	**Metformin + Gliclazide**	500mg+80 mg	120	13 ₹ (0.15 $)	7
4	**Metformin + Glibenclamide**	500mg+5 mg	170	5 ₹ (0.05 $)	9
Metformin + Meglitinides					
1	**Metformin + Repaglinide**	500mg+ 2 mg	15.6	16.8 ₹ (0.19 $)	7
2	**Metformin + Nateglinide**	500mg+ 60 mg	311	19.7 ₹ (0.23 $)	5
Metformin + α-Glucosidase inhibitors					
1	**Metformin + Acarbose**	500mg+25 mg	114.3	13 ₹ (0.15 $)	7
2	**Metformin + Voglibose**	500mg+ 0.3 mg	180	14.4 ₹ (0.17 $)	14

The number of pharmaceutical companies manufacturing each drug was also recorded. The analysis revealed that metformin + dapagliflozin exhibited the highest cost variation at 436.2%, being produced by 14 pharmaceutical companies. Following this, metformin + glipizide showed the second-highest cost variation at 327%. In contrast, metformin + saxagliptin demonstrated the lowest CV% at 11.43%, closely followed by metformin + empagliflozin with a CV% of 25.39% (Figure 1).

Figure 1. Comparison of the cost variation of metformin-based dual FDCs



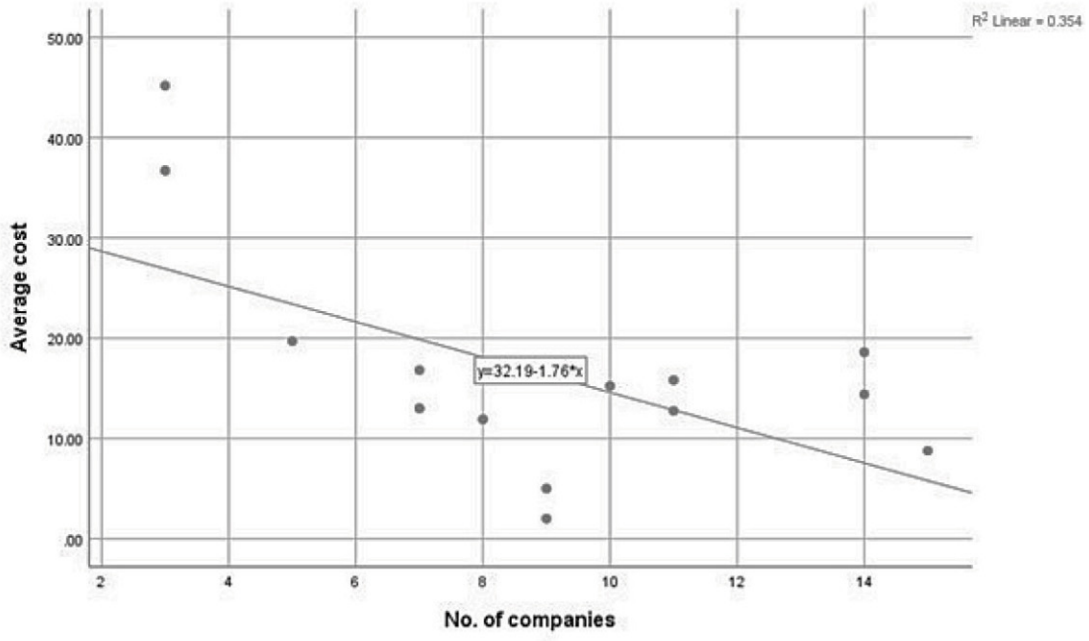
Average Cost Analysis

Among the FDC antidiabetic medications analyzed, metformin + saxagliptin exhibited the highest average cost of 45.16 rupees (0.52$) per tablet. This was followed by metformin + empagliflozin, with an average cost of 36.70 rupees (0.42$) per tablet. Conversely, metformin + glipizide was identified as the most economical FDC across all groups, averaging merely 2.00 rupees (0.02$) per tablet.

Correlation Analysis

A statistically significant negative relationship was observed between the average cost of drugs and the total number of manufacturing companies ($r = -0.595$, $p = 0.019$*) and in the metformin + DPP4is group ($r = -0.900$, $p = 0.037$*) (Figure 2). Conversely, the correlation between the CV% and the number of manufacturing companies across all groups was positive but not statistically significant ($r = 0.436$, $p = 0.106$).

Figure 2. Pearson correlation between the average cost and the number of manufacturing companies



Discussion

Metformin is widely recognized as the primary pharmacological intervention for newly diagnosed T2DM. However, due to the progressive nature of T2DM, over 90% of patients will eventually require additional medications beyond metformin monotherapy to effectively manage their blood glucose levels. When prescribed as an FDC, metformin is typically administered in daily dosages ranging from 250 mg to 2550 mg. (14,15)

A study by Lokhandwala et al. (13) demonstrated that patients receiving FDCs exhibited greater persistence and adherence compared to those on loose-dose combinations.

Given the rising trend of prescribing metformin-based FDCs in India (16,17), our study focused on analyzing cost variations among dual FDCs containing metformin 500 mg with other OADs.

For over five decades, SUs have been widely co-prescribed with metformin in the management of T2DM due to their cost-effectiveness and significant therapeutic efficacy (18). However, it is important to note that SUs are also linked to an increased incidence of hypoglycemia and a higher risk of cardiovascular complications. (19, 20)

Research conducted across India consistently indicates that metformin + SUs FDCs are the most frequently prescribed treatments for diabetes, with prescription rates ranging from 40% to 80% (9,21,22,23,24).

For the past decade, a notable paradigm shift has been observed in the prescribing patterns for T2DM. Physicians are increasingly favoring newer agents, specifically DPP-4is and SGLT2is, as add-on therapies to metformin, while moving away from SUs and other established OADs. (25)

The International Diabetes Federation (IDF) guidelines suggest that an initial combination therapy for diabetes management may include metformin + DPP-4is or metformin + SGLT2is. These more recently developed medications offer broad-ranging beneficial effects on both cardiovascular and renal functions.

In our study, the metformin + dapagliflozin combination demonstrated the highest cost variation. This finding aligns with a previous study conducted in India, which also reported a substantially high CV% of 1591% for the same combination. However, the Indian study also indicated that the metformin + SUs group exhibited the highest CV%, a finding that contradicts the results of our current research. According to a recent study, the metformin + empagliflozin combination exhibits the lowest cost variability, a finding consistent with the results of the current research. (26)

Among FDCs, the metformin + saxagliptin combination incurred the highest average overall cost, followed by metformin + empagliflozin. Conversely, metformin + glipizide 5 mg was identified as the most economical FDC.

The two most recently introduced FDC groups, DPP4is and SGLT2is, exhibited both the highest average costs and the most significant cost variations. This trend may be attributed to their increasing prescription rates, which are nearing those of SU FDCs, despite the inherently higher cost of DPP4is and SGLT2is. (27) This rise in prescriptions is largely driven by the private healthcare sector in India, which accounts for approximately 80% of diabetes care in the country. (28)

The comprehensive statistical analysis revealed a significant inverse correlation between the average cost of drugs and the number of manufacturing companies. This statistically significant correlation was also observed specifically within the metformin + DPP-4is group. This inverse relationship implies that pharmaceutical companies are responsive to price competition. A decrease in prices could incentivize more companies to enter the market, subsequently intensifying downward pricing pressure. Conversely, a reduction in the number of manufacturers may lead to increased market power, enabling the remaining companies to establish higher prices. A limited number of manufacturers typically signifies a concentrated market, granting existing players greater control over pricing strategies. This phenomenon is particularly evident with newer drugs, where patents or proprietary formulations often restrict market competition.

To lower the cost of metformin-based FDCs in India, regulatory authorities should promote market competition. This can be achieved by expediting the approval process for generic and biosimilar versions of these drugs. The integration of these medications into the National List of Essential Medicines (NLEM) would significantly empower the National Pharmaceutical Pricing Authority (NPPA) to regulate the prices of newer metformin FDCs in India. This regulatory oversight is expected to incentivize more pharmaceutical companies to manufacture these drugs. Consequently, based on the findings of our study, this would lead to increased prescriptions by physicians without substantially impacting treatment costs.

This could promote the integration of metformin-based FDCs into government hospital supply chains, thereby benefiting a substantial number of patients seeking diabetes care at these facilities. Furthermore, it would alleviate the financial burden on patients relying on private clinics for metformin-based FDCs to manage their diabetes.

Limitations

Our research exclusively utilized data on FDCs containing metformin 500 mg from two verified online sources. An intragroup analysis of these FDCs was not conducted.

Conclusion

Our research identified the highest cost variation and average cost associated with SGLT2is and DPP4is FDCs with metformin, respectively. The findings underscore the critical need for these drug combinations to be urgently incorporated into the NLEM. Such inclusion would empower the NPPA to effectively regulate and reduce their prices. Consequently, this measure could enhance their availability within government supply chains and alleviate the financial burden on patients seeking treatment in private healthcare centers. Ultimately, this strategy aims to ensure that a substantial portion of India's diabetic population can access and benefit from these innovative drug combinations earlier in their treatment regimen.

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PLEASE CITE THIS PAPER AS:

Shinde M, Kushwah A. Cost Variation Analysis of Metformin-Based Dual Fixed-Dose Combinations Prescribed in India. J Pharm Care. 2025;13(3):217-223. DOI:10.18502/jpc.v13i3.20324