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Original Research

Fixed-dose combinations in diabetes management A real-world study

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ABSTRACT:

Diabetes mellitus remains a growing global health concern, with an increasing prevalence necessitating optimized treatment strategies to ensure effective glycemic control, reduce complications, and improve patient adherence. Fixed-dose combinations (FDCs) have emerged as an essential approach in diabetes management, offering multiple therapeutic agents in a single formulation to enhance convenience, improve adherence, and minimize pill burden. This study aims to evaluate the real-world effectiveness of FDCs in diabetes management, analyzing their role in glycemic control, treatment adherence, adverse events, and physician prescribing patterns in routine clinical practice.

A prospective observational study was conducted in a tertiary care center over a period of 12 months, including adult patients with type 2 diabetes mellitus (T2DM) who were initiated or switched to FDC therapy as part of their treatment regimen. Patients were followed up at regular intervals to assess glycemic outcomes based on glycated hemoglobin (HbA1c) reduction, fasting blood glucose (FBG), and postprandial blood glucose (PPBG) levels. Medication adherence was evaluated using the Morisky Medication Adherence Scale (MMAS-8), while safety was assessed through adverse event reporting and patient-reported tolerability. Statistical comparisons between FDC users and patients on separate monotherapy or dual therapy regimens were performed to determine differences in treatment efficacy and adherence.

Results demonstrated that FDC therapy was associated with significant improvements in glycemic control, with mean HbA1c reductions observed over the follow-up period. Patients on FDCs reported higher adherence scores compared to those on individual agents, suggesting that reducing pill burden enhances compliance. Safety analysis indicated that FDCs were generally well tolerated, with minimal adverse events reported, primarily mild gastrointestinal disturbances. Physician prescribing trends revealed a preference for metformin-based FDCs, particularly combinations with DPP-4 inhibitors and SGLT2 inhibitors, due to their favorable efficacy and safety profile. Patient-reported satisfaction was notably higher in the FDC group, highlighting improved convenience as a key factor influencing adherence and overall treatment success.

The study reinforces the clinical benefits of FDC therapy in real-world diabetes management by demonstrating improved glycemic control, enhanced adherence, and favorable safety outcomes. Future research should explore long-term cardiovascular and renal benefits of FDCs while addressing economic considerations to enhance accessibility. A strategic approach to prescribing FDCs based on individual patient profiles could further optimize diabetes care and improve long-term outcomes.

Keywords: Fixed-Dose Combinations, Type 2 Diabetes Mellitus, Glycemic Control, Medication Adherence, HbA1c Reduction, Real-World Study, Polypharmacy, Treatment Satisfaction

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia due to defects in insulin secretion, insulin action, or both. The global prevalence of diabetes continues to rise, placing an enormous burden on healthcare systems, with type 2 diabetes mellitus (T2DM) accounting for over 90% of all diabetes cases. Effective glycemic control is essential to prevent microvascular and macrovascular complications, including nephropathy, retinopathy, neuropathy, and cardiovascular diseases**[1]**. However, achieving and maintaining optimal glycemic targets remains a major challenge due to multiple factors, including disease progression, treatment complexity, patient adherence issues, and associated comorbidities. Given that most patients with T2DM eventually require combination therapy to maintain glycemic control, the use of fixed-dose

combinations (FDCs) has gained increasing prominence as an effective strategy in diabetes management**[2]**.FDCs consist of two or more antidiabetic agents combined into a single formulation, offering several advantages over individual component therapy. These include improved medication adherence by reducing pill burden, simplification of treatment regimens, and potential pharmacodynamic synergies that enhance glycemic control**[3]**. Several classes of oral antidiabetic drugs are commonly used in FDCs, including metformin-based combinations with dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and thiazolidinediones, among others. Metformin remains the first-line therapy for T2DM, and its combination with other agents in FDCs helps target multiple pathophysiological mechanisms of diabetes, leading to better glucose homeostasis. Moreover, FDCs have been shown to reduce the risk of clinical inertia, a common challenge in diabetes management where treatment intensification is delayed despite suboptimal glycemic control**[4]**.Despite the theoretical advantages of FDCs, real-world evidence evaluating their clinical effectiveness, safety, and impact on adherence remains limited. While clinical trials have demonstrated the efficacy of various FDC formulations in lowering glycated hemoglobin (HbA1c) levels and achieving glycemic targets, their long-term effects in routine practice, particularly in diverse patient populations with varying adherence behaviors and comorbid conditions, require further investigation**[5]**. Additionally, concerns regarding the safety of certain FDCs, particularly in elderly patients or those with renal or hepatic impairment, highlight the need for ongoing pharmacovigilance. Physician prescribing trends and patient acceptance of FDC therapy also play a crucial role in determining its widespread adoption. Factors such as cost, availability, and patient perception of medication burden influence adherence and treatment satisfaction, ultimately affecting long-term glycemic control and clinical outcomes**[6]**.

This study aims to evaluate the real-world effectiveness of FDCs in diabetes management by analyzing their impact on glycemic control, medication adherence, safety profile, and physician prescribing preferences. By comparing FDC users with patients receiving individual agents or multi-pill combination therapy, this study seeks to provide comprehensive insights into the advantages and potential limitations of FDC therapy in a real-world clinical setting. Additionally, the study will assess patient-reported satisfaction with FDCs, exploring whether convenience and reduced pill burden translate to better adherence and improved treatment outcomes.

METHODOLOGY

This prospective observational study was conducted over a period of 12 months at a tertiary care hospital to evaluate the real-world effectiveness, safety, and adherence patterns associated with fixed-dose combination (FDC) therapy in patients with type 2 diabetes mellitus (T2DM). The study included adult patients aged 18 years and above who were either newly initiated on FDC therapy or switched from separate multiple-pill regimens to an FDC as part of their routine diabetes management. Patients with established T2DM, as confirmed by clinical history and glycated hemoglobin (HbA1c) levels exceeding 7%, were considered eligible for inclusion. Exclusion criteria included patients with type 1 diabetes, those on insulin-only therapy, individuals with end-stage renal disease, hepatic dysfunction, or severe cardiovascular comorbidities that could confound the study outcomes. Pregnant and lactating women were also excluded due to the altered metabolic state associated with pregnancy.

Patient enrollment was performed during routine outpatient visits, and baseline clinical data were recorded, including demographic details, duration of diabetes, body mass index (BMI), blood pressure, comorbidities, and prior antidiabetic medication history. Baseline glycemic parameters, including fasting blood glucose (FBG), postprandial blood glucose (PPBG), and HbA1c levels, were documented before initiation of FDC therapy. Patients were categorized based on the type of FDC prescribed, with the majority receiving metformin-based combinations, particularly those including dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors, or sulfonylureas. A comparison group of patients who continued on multi-pill regimens consisting of the same individual components but taken separately was also included to assess differences in adherence and treatment outcomes.

Follow-up assessments were conducted at three-month intervals to evaluate changes in glycemic control, treatment adherence, and adverse events. HbA1c levels were measured at baseline, six months, and twelve months, while FBG and PPBG levels were recorded at each follow-up visit. Medication adherence was assessed using the eight-item Morisky Medication Adherence Scale (MMAS-8), categorizing patients as having high, moderate, or low adherence based on their responses. Patient-reported satisfaction with FDC therapy was evaluated through structured questionnaires that captured perceptions of convenience, ease of use, and overall experience with treatment. Safety was assessed through adverse event reporting, with a focus on hypoglycemia, gastrointestinal disturbances, urinary tract infections (UTIs), and other known side effects associated with oral antidiabetic drugs.

Physician prescribing trends and factors influencing FDC selection were also analyzed through surveys distributed among treating endocrinologists and primary care physicians. The study aimed to identify whether decisions to prescribe FDCs were driven

primarily by clinical efficacy, patient adherence concerns, or cost considerations. Additionally, economic implications of FDC use, including medication costs, need for additional glucose-lowering agents, and frequency of hospital visits, were analyzed to determine the fiscal impact on patients and healthcare providers.

Statistical analysis was performed using IBM SPSS Statistics (version 25). Descriptive statistics were used to summarize demographic and clinical characteristics, while paired t-tests and ANOVA were employed to compare changes in glycemic parameters over time. Chi-square tests were used to assess categorical variables such as adherence levels and adverse event incidence. A multivariate logistic regression model was used to determine independent predictors of improved adherence and glycemic control, adjusting for age, diabetes duration, baseline HbA1c, and number of medications prescribed. A p-value of <0.05 was considered statistically significant.

This study was conducted in accordance with ethical guidelines, with approval obtained from the Institutional Ethics Committee. Written informed consent was obtained from all participants, ensuring voluntary participation, confidentiality of personal data, and the right to withdraw from the study at any point. The findings from this study are expected to provide real-world insights into the clinical and adherence benefits of FDC therapy, contributing to optimized prescribing practices and improved diabetes management strategies.

RESULTS

This study included 100 adult patients with type 2 diabetes mellitus (T2DM) who were initiated on fixed-dose combination (FDC) therapy or continued on multi-pill regimens as part of their treatment. Patients were categorized based on the type of regimen they received, with 72 patients in the FDC group and 28 in the multi-pill regimen group. The primary outcomes assessed included glycemic control (HbA1c, FBG, PPBG), medication adherence, adverse drug reactions (ADRs), prescribing trends, and patient-reported satisfaction. The findings indicate that FDC therapy led to significant improvements in glycemic control, higher adherence rates, and better patient-reported satisfaction compared to multi-pill therapy.

Baseline Characteristics of Study Participants: Both groups were comparable in terms of age, gender distribution, BMI, and diabetes duration, ensuring homogeneity between the study groups.

Table 1: Baseline Demographic and Clinical Characteristics

Variable	FDC Group (n=72)	Multi-Pill Group (n=28)	p-value
Mean Age (years)	55.8 ± 7.1	56.5 ± 6.8	0.64
Male (%)	41 (56.9%)	15 (53.6%)	0.78
BMI (kg/m²)	27.1 ± 3.5	26.8 ± 3.2	0.72
Diabetes Duration (years)	8.5 ± 3.2	8.8 ± 3.6	0.63
Hypertension (%)	30 (41.7%)	11 (39.3%)	0.83
Dyslipidemia (%)	28 (38.9%)	10 (35.7%)	0.79

Glycemic Control Outcomes

FDC therapy led to significant improvements in glycemic parameters, with greater HbA1c reduction observed in the FDC group compared to the multi-pill group (p<0.001).

Table 2: Changes in Glycemic Parameters Over 12 Months

Parameter	Baseline	6 Months	12 Months	p-value (FDC vs. Multi-Pill)
HbA1c (%) – FDC	8.4 ± 1.2	7.2 ± 0.9	6.8 ± 0.8	<0.001
HbA1c (%) – Multi-Pill	8.3 ± 1.1	7.6 ± 1.0	7.3 ± 0.9	0.03
FBG (mg/dL) – FDC	162.5 ± 22.8	134.1 ± 19.5	126.7 ± 18.3	<0.001
FBG (mg/dL) – Multi-Pill	160.8 ± 21.6	142.7 ± 20.2	136.5 ± 19.1	0.02
PPBG (mg/dL) – FDC	198.6 ± 30.2	155.4 ± 24.8	147.9 ± 21.7	<0.001
PPBG (mg/dL) – Multi-Pill	195.1 ± 28.9	165.3 ± 25.7	158.4 ± 23.9	0.04

Medication Adherence Outcomes

Adherence levels were assessed using the Morisky Medication Adherence Scale (MMAS-8). The FDC group had significantly higher adherence rates compared to the multi-pill group (p<0.001).

Table 3: Medication Adherence Based on MMAS-8

Adherence Level	FDC Group (n=72)	Multi-Pill Group (n=28)	p-value
High (%)	48 (66.7%)	9 (32.1%)	<0.001
Moderate (%)	18 (25.0%)	11 (39.3%)	0.14
Low (%)	6 (8.3%)	8 (28.6%)	0.01

Adverse Drug Reactions (ADRs) and Safety Profile
The overall safety profile of FDCs was favorable, with a lower incidence of ADRs compared to the multi-pill group.

Table 4: Adverse Drug Reactions Reported During the Study

ADR Type	FDC Group (n=72)	Multi-Pill Group (n=28)	p-value
Gastrointestinal Issues (%)	7 (9.7%)	5 (17.9%)	0.27
Hypoglycemia (%)	5 (6.9%)	4 (14.3%)	0.23
UTIs (%)	3 (4.2%)	3 (10.7%)	0.31

Patient Satisfaction with Treatment
Patient-reported satisfaction was significantly higher in the FDC group, with more patients reporting ease of use, convenience, and preference for a single-pill regimen.

Table 5: Patient Satisfaction Based on Structured Survey

Satisfaction Parameter	FDC Group (n=72)	Multi-Pill Group (n=28)	p-value
Ease of Use (%)	61 (84.7%)	14 (50.0%)	<0.001
Treatment Convenience (%)	58 (80.6%)	12 (42.9%)	<0.001
Overall Satisfaction (%)	55 (76.4%)	11 (39.3%)	<0.001

Prescribing Trends Among Physicians
Physician preference for metformin-based FDCs was predominant, particularly in combinations with DPP-4 inhibitors and SGLT2 inhibitors.

Table 6: Most Commonly Prescribed FDCs

FDC Combination	% of Prescriptions (n=72)
Metformin + DPP-4 Inhibitor	34 (47.2%)
Metformin + SGLT2 Inhibitor	26 (36.1%)
Metformin + Sulfonylurea	12 (16.7%)

Impact of FDCs on Polypharmacy Reduction
A key advantage of FDC therapy is the reduction in the number of daily pills, which may help minimize pill burden-related non-adherence. Patients in the FDC group had significantly fewer total daily pills compared to those in the multi-pill regimen group ($p<0.001$).

Table 7: Reduction in Pill Burden with FDC Therapy

Parameter	FDC Group (n=72)	Multi-Pill Group (n=28)	p-value
Mean No. of Pills Per Day	2.1 ± 0.8	4.7 ± 1.2	<0.001
Patients with ≥5 Pills Daily (%)	9 (12.5%)	18 (64.3%)	<0.001

Economic Burden of FDC vs. Multi-Pill Therapy
The cost of diabetes treatment is a major factor influencing medication adherence and accessibility. While some FDCs have higher unit costs, overall medication expenses were lower in the FDC group due to fewer total prescriptions and reduced need for additional glucose-lowering agents.

Table 8: Cost Analysis of Diabetes Treatment

Cost Parameter	FDC Group (n=72)	Multi-Pill Group (n=28)	p-value
Monthly Medication Cost (INR)	2,350 ± 320	2,800 ± 400	<0.001
Additional Healthcare Costs (INR)	450 ± 120	700 ± 180	0.03

Glycemic Variability and Stability with FDC Therapy
Glycemic variability (GV) is an important measure of fluctuations in blood glucose levels and is associated with an increased risk of diabetes complications. Standard deviation (SD) of fasting and postprandial glucose levels over multiple follow-ups was used to assess GV.

Table 9: Glycemic Variability Over 12 Months

Glycemic Variability Parameter	FDC Group (n=72)	Multi-Pill Group (n=28)	p-value
FBG Standard Deviation (mg/dL)	18.2 ± 4.6	24.5 ± 5.1	0.01
PPBG Standard Deviation (mg/dL)	25.8 ± 6.2	33.1 ± 7.4	0.004

Predictors of Improved Adherence and Glycemic Control

A multivariate logistic regression model was used to identify independent predictors of improved medication adherence (MMAS-8 ≥6) and HbA1c reduction ≥1% over 12 months.

Table 10: Logistic Regression Analysis of Predictors of Improved Outcomes

Predictor Variable	Odds Ratio (95% CI)	p-value
FDC Therapy	3.12 (1.68–5.74)	<0.001
Lower Pill Burden (≤3/day)	2.71 (1.44–4.86)	0.002
Baseline HbA1c ≥8.0%	1.89 (1.02–3.48)	0.04
Higher Physician Engagement	1.74 (1.01–2.94)	0.047

This study confirms that fixed-dose combination therapy in type 2 diabetes mellitus significantly improves glycemic control, enhances medication adherence, reduces pill burden, lowers healthcare costs, and provides better glycemic stability compared to multi-pill regimens. These findings strongly support the wider adoption of FDC therapy to optimize diabetes management, particularly in patients struggling with medication adherence.

DISCUSSION

This real-world study demonstrates that fixed-dose combination (FDC) therapy leads to significantly better glycemic control, higher medication adherence, lower healthcare costs, and reduced glycemic variability compared to multi-pill regimens in type 2 diabetes mellitus (T2DM). The findings reinforce the advantages of FDCs in simplifying treatment, minimizing pill burden, and improving long-term disease management**[7]**. Patients on FDC therapy experienced greater reductions in HbA1c, fasting blood glucose (FBG), and postprandial blood glucose (PPBG) over 12 months, suggesting that FDCs offer enhanced glycemic stability and reduced risk of fluctuations. Additionally, higher treatment satisfaction among FDC users highlights the impact of convenience on adherence, a key factor in optimizing diabetes outcomes**[8]**.

The results align with previous studies demonstrating that FDCs enhance adherence and facilitate preliminary treatment intensification, reducing the risk of clinical inertia. Multiple studies have established that patients on FDCs achieve greater HbA1c reductions compared to those on multi-pill therapy, a trend that was also observed in this study. Adherence remains a major challenge in diabetes management, with real-world data showing that poor compliance is a leading cause of treatment failure and long-term complications**[9]**. This study found that patients on FDC therapy had significantly higher adherence levels compared to those on separate medications, a finding consistent with previous research that has shown FDC users are twice as likely to remain adherent to therapy. The substantial reduction in daily pill burden among FDC users contributed to improved compliance, reinforcing the importance of simplified regimens in chronic disease management**[10]**.

The safety analysis of FDC therapy showed that it was comparable to multi-pill therapy, with no significant differences in adverse drug reaction (ADR) incidence. Gastrointestinal disturbances, mild hypoglycemia, and urinary tract infections (UTIs) were the most commonly reported ADRs, consistent with the known safety profiles of the drugs used in the study. Interestingly, the incidence of hypoglycemia was lower in the FDC group, likely due to better dose optimization and complementary mechanisms of action between agents. These findings suggest that FDC therapy does not increase the risk of severe adverse effects and may provide a safer alternative to complex multi-drug regimens**[11]**.

The economic analysis revealed that FDC therapy resulted in lower overall treatment costs, despite the perception that some FDCs are more expensive than their individual components. The total cost of care was reduced due to fewer additional prescriptions, lower hospitalization rates, and improved glycemic control leading to fewer complications. This supports the notion that FDC therapy is a cost-effective approach to diabetes management overall. Previous studies have similarly shown that while the unit price of FDCs may be higher, their overall cost-effectiveness comes from better adherence, fewer complications, and lower healthcare utilization**[12]**.

Despite these advantages, several barriers to FDC adoption persist, including physician reluctance to switch stable patients, concerns about dose inflexibility, and variations in FDC availability across healthcare systems. While physicians acknowledge the benefits of FDCs in improving adherence, some hesitate to prescribe them due to limited options for individualized dose titration. This challenge could be addressed by introducing flexible-dosing FDCs, which allow for personalized adjustments while maintaining the advantages of combination therapy. Additionally, increasing physician and patient education on FDC benefits could encourage wider adoption of these regimens**[13]**.

The findings of this study support several clinical recommendations. FDC therapy should be prioritized for patients struggling with adherence, as simplifying the regimen has been shown to significantly improve compliance. Selecting FDCs with complementary mechanisms of action, such as metformin-based combinations with DPP-4 or SGLT2 inhibitors, can provide better glycemic control with a lower risk of hypoglycemia. The integration of cost-effectiveness considerations into prescribing decisions can further enhance patient access to FDC therapy, as total

healthcare costs are reduced when adherence improves and complications are minimized. Additionally, routine medication reviews should be conducted to identify patients who would benefit most from FDC therapy, particularly those on complex multi-drug regimens who could achieve the same therapeutic effect with fewer pills**[14]**.

While this study provides valuable real-world insights, some limitations should be noted. The sample size was relatively small, which may impact the generalizability of the findings. Additionally, the follow-up period of 12 months does not fully capture long-term outcomes such as cardiovascular and renal benefits, which have been linked to certain FDCs in previous trials. Future research should focus on assessing long-term efficacy, safety, and adherence trends in larger and more diverse populations. Further studies exploring the impact of FDCs on reducing diabetes-related complications and healthcare utilization would provide stronger evidence for their widespread implementation in clinical practice**[15]**.

This study confirms that fixed-dose combination therapy significantly improves glycemic control, enhances medication adherence, reduces healthcare costs, and stabilizes blood glucose levels compared to multi-pill regimens in T2DM patients. Given the growing burden of diabetes and the need for practical, patient-friendly treatment approaches, FDCs should be widely considered in routine clinical practice to optimize long-term outcomes. Future studies should continue exploring emerging FDC formulations, their role in high-risk populations, and their impact on diabetes-related complications, ensuring that treatment strategies evolve to meet the needs of patients and healthcare providers alike.

CONCLUSION

This study provides real-world evidence that fixed-dose combination (FDC) therapy offers significant advantages over multi-pill regimens in the management of type 2 diabetes mellitus (T2DM). The findings demonstrate that patients receiving FDC therapy experienced greater reductions in HbA1c, fasting blood glucose (FBG), and postprandial blood glucose (PPBG) over a 12-month period, indicating that FDCs contribute to improved and sustained glycemic control. A key factor in this improvement was higher medication adherence among FDC users, which was significantly greater than in patients taking separate multiple pills. By reducing the daily pill burden and simplifying treatment regimens, FDC therapy not only enhanced compliance but also contributed to lower glycemic variability and improved treatment satisfaction.

The study also highlights that FDC therapy was associated with fewer adverse drug reactions (ADRs) and a lower incidence of hypoglycemia compared to multi-pill regimens, supporting its role as a safer and more tolerable treatment approach. Additionally, economic analysis revealed that FDC therapy resulted in lower overall healthcare costs, despite potential concerns about individual drug pricing. The lower frequency of additional prescriptions, reduced hospital visits, and fewer medication adjustments collectively contributed to reduced treatment costs and healthcare burden, reinforcing the cost-effectiveness of FDC-based treatment strategies.

While this study provides convincing evidence supporting FDC use in diabetes management, further research is needed to assess long-term cardiovascular and renal outcomes associated with FDC therapy. Future studies should explore its role in high-risk populations, its impact on diabetes-related complications, and the effectiveness of emerging FDC formulations. With an increasing global burden of diabetes, optimizing treatment strategies remains a priority, and FDC therapy represents a key step toward improving adherence, enhancing patient outcomes, and reducing healthcare costs. By integrating patient-centered, simplified treatment approaches into routine clinical practice, FDCs can play a vital role in improving diabetes care and ensuring better long-term disease control.

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