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ASSESSMENT OF SAFETY AND EFFICACY OF GENERIC AND BRANDED METFORMIN

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ABSTRACT

Branded drugs are the original products developed by a pharmaceutical company. Generic drugs are equivalents of branded drugs and have same active ingredients and dosage form. Type II Diabetes Mellitus is usually treated with oral hypoglycemics, Metformin being the most prescribed; either in combination or as monotherapy. This study was conducted to assess the safety and efficacy of both branded and generic Metformin. Data regarding adverse effects, laboratory parameters: Random Blood Sugar and Glycosylated Hemoglobin was collected at regular intervals. To evaluate safety, participants were enquired about the Adverse Drug Reactions (ADRs) they faced after starting metformin. The most common ADRs reported was diarrhoea (56.7%), followed by acidity and sour stomach (43.3%), pain or numbness in knees and joints (40%), dizziness (23.3%) light headedness and tiredness (13.3%.) To compare the efficacy of branded versus generic metformin, participants' baseline RBS and HbA1c values were recorded and compared to understand the difference over a period of three months. There was a mean difference of 63.53 in branded users RBS over a period of 3 months and 49.733 difference in generic metformin users, this difference was found statistically significant, which indicates that branded metformin showed a slightly better action on RBS levels. Comparing HbA1c values, branded users showed a mean difference of 0.766 over 3 months, whereas generic users showed a difference of 0.4 over 3 months, obtaining their p values the difference found out was statistically insignificant implying that the action of both branded and generic metformin was same in HbA1c levels. According to analysis of the data obtained, we infer that the safety of both branded and generic metformin is same. Branded metformin showed

marginally better action on RBS levels and there was no difference in HbA1c levels of both branded and generic metformin users.

KEYWORDS: Generics, Branded, Metformin, Awareness, Safety, Efficacy, Quality.

INTRODUCTION

Type II Diabetes Mellitus is a chronic metabolic disorder, which is characterized by persistent hyperglycemia.[1] Incidence of T2DM is increasing globally and given the scenario of India, there has been a steady increase in the last few years. The prevalence of type 2 diabetes mellitus is 2.4% in rural population and 11.6% in urban population. The prevalence of diabetes in India has risen from 7.1% in 2009 to 8.9% in 2019.[2]

According to various studies conducted, the most common prescribed oral hypoglycemic is Metformin, which may or may not be prescribed with other add on drugs. Among the single drug (monotherapy) prescriptions, metformin was most prescribed (16.4% of prescriptions). Combination of metformin with glimepiride (Sulfonylurea and biguanide combination drugs) was the most seen dual drug regimen (18.8% of prescriptions)[3] followed by metformin given with various DPP IV inhibitors chiefly teneligliptin (5.4% of prescriptions). Among triple drug regimens, combinations of metformin, glimepiride, and a DPP IV inhibitor (13.76% prescriptions) were most common followed by metformin and glimepiride and pioglitazone (3.9% prescriptions).[4]

Since Type II DM is a lifelong, chronic disorder that requires continuous use of medication, it is very necessary to investigate the cost effectiveness of the medications prescribed so that the economic burden of a patient does not increase and affect medication adherence of the patient.

Patients are dependent on physicians for medicine prescriptions and have little knowledge of the price variations among branded and generic medicines.[5] One of the ways of achieving this is by using Generic Medicines, a generic drug is a medication created to be the same as an existing approved brand name drug in dosage form, safety, strength, route of administration, Quality and Performance characteristics.

Generic drugs provide the opportunity for major savings in healthcare expenditure since they are usually substantially lower in price than the innovator brands. However, generic substitution should not be based solely on the initial cost of treatment but on the overall cost

effectiveness of pharmacological treatment. As a result, a standard has been set for generic substitution. Interchangeability is permitted when the generic product demonstrates bioequivalence and therapeutic equivalence with the innovator.[6]

Physicians are apprehensive regarding the quality of generic drugs and have concerns about their reliability as well as interchange of certain drug categories. Although the generic medicines are bio-equivalents of their innovator counterparts and are produced in similar facilities according to good manufacturing practices, these are widely believed as inferior in their therapeutic efficacy and quality to *branded* products.[7]

Physician scepticism about generic medication has been associated with lack of pharmaceutical marketing.[8]

While the inherent scepticism is not a fake one, generics and branded medicines differ based on their excipients and studies suggested that a possible explanation in clinical difference between brand formulation and a generic one might be represented by the difference in excipients Moreover, several studies documented that a difference in excipients is related with the loss of response during treatment with the generic formulations.[9]

Currently, almost all medicines in India are sold under a brand (trade) name and medicines are called as *branded* medicines. In India, many pharmaceutical companies manufacture two types of products for the same molecule, i.e., the *branded* product which they advertise and push through doctors and *branded-generic* which they expect retailers to push in the market. The so-called *branded* medicines in India are manufactured and promoted by multinationals or by reputed Indian manufacturers. *Generic*s, on the other hand, are not promoted or advertised by the manufacturer.[10]

While the bioequivalence of Generic and Branded drugs has been proved many times, through invitro studies and the performance of the branded and generic products of metformin tablets is similar and no significant differences were observed in the dissolution parameters of the branded and generic products.[11] A certain brand loyalty ingrained in patients and the lack of awareness does not allow them to fully trust Generic medicines.

Branded medicines on the other hand are often exuberantly priced due to their expensive advertising and excipients which explains the difference in prices even after the active ingredient and their dose remains the same.

When a firm creates a new drug, it must go through and pass a series of tests and evaluations to guarantee that it will cure the disease it claims to treat while also being safe to use in humans. Pharmaceutical corporations are given the exclusive right to make and market pharmaceuticals for a set length of time since they spend a lot of money developing new drugs. It is protected by a patent. So, the brand-name drug is the most well-known and trusted drug.[12]

Jan Aushadhi is a government run scheme in India that allows for pharmaceuticals to make inexpensive and high-quality medications a reality in India. Rising healthcare cost in India has made it difficult for the poor section of the society to avail even basic health services. Keeping this in mind, Jan Aushadhi scheme was launched to ensure medicines can be availed by anyone and at a very cheaper price.[13]

To put it another way, generic drugs are non-branded medications that have the same efficacy as their more expensive branded equivalents. Negative perceptions of generic medicines and preferential promotion of branded medicines over generics by pharmaceutical companies could influence prescriber behavior and affect trust in healthcare provided in public services.[14] Hence, the general notion and doubt regarding the quality and efficacy of the generic version of medicines needs to be expunged.[15]

Safety of a drug refers to the frequency of adverse drug effects (i.e., physical or laboratory toxicity that could possibly be related to the drug) that are *treatment emergent*—that is, they emerge during treatment and were not present before treatment, or they become worse during treatment compared with the pre-treatment state. In previous studies the most common ADRs studied included gastrointestinal adverse events, especially diarrhoea, nausea, and abdominal discomfort, acidity, pain in joints and more.[16] Efficacy of a drug or a treatment is often determined by how they affect clinical endpoints. Clinical endpoints must be specific and relevant to the drug or disease. To compare two endpoints, they must be: A) Clinically relevant B) Sensitive to treatment effect C) Measurable and interpretable.[17]

It is also necessary for us to understand patients overall Quality of Life and humanistic outcomes. It is also necessary for us to understand the economic reasons and outcomes that may often determine why the patient is using either branded or generic medicine. Based on ECHO model of pharmacoeconomic, (E)economic outcomes, (C)clinical outcomes, (H)Humanistic outcomes. Humanistic outcomes include 1) symptom status, functional status,

and 3) quality of life (QOL), Often these outcomes are interrelated and overlap one another.[18,19] The idea behind conducting this study was to make patients aware that both branded and generic metformin have the same composition and so they can switch to generic medicine if required and to also ensure that burden to buy an expensive brand drug does not become a reason for patient medication non-adherence.

METHODOLOGY

The study was designed as a prospective comparison study and was carried out at two sites; a tertiary care hospital (CSI Holdsworth Memorial (Mission) Hospital, Mysore) and a generic community pharmacy (Pradhan Mantri Bhartiya Jan Aushadhi Kendra, Bannimantap, Mysore, Karnataka) for a period of 6 months. Data was collected from patient prescriptions and case sheets. Data collection forms were designed and patients were interviewed.

Inclusion criteria

- Patients diagnosed with Type 2 Diabetes Mellitus
- Patients currently prescribed with Metformin (monotherapy or in combination)
- Patients willing to take HbA1c test

Literature search was done using various databases and relevant articles were used for reference. The collected data was statistically analyzed by a biostatistician with the help of the STATA (Statistics and Data) software. STATA is a statistical software which enables to analyses, manage and produce graphical representations of data. In this study, it was used to compare the differences in the results between generic group and branded group.

RESULTS

This study enrolled 30 patients, with 15 using Branded Metformin and 15 using Generic Metformin, and data was collected from both Mission Hospital, Mysore and Jan Aushadhi Kendra, Mysore using a well-designed data collection form consisting of 26 questions.

The study included 30 participants, out of which 17 (56.7%) were male and 13 (43.3%) were female. The age range of participants was 30-70 years, with the most common age group being 41-50 years (12 participants; 40%). The duration of T2DM diagnosis varied among participants, with 14 (46.7%) having been diagnosed for 1-5 years, 13 (43.3%) being diagnosed in the last 6-10 years, and 3 (10%) having been diagnosed for more than 11 years.

Table 1: Demographic details of participants.

Demographic Details	Frequency (n=30)	Percentage (%)
Gender:		
Female	13	43.30
Male	17	56.70
Age (In years):		
30-40	02	06.66
41-50	12	40.00
51-60	08	26.66
61-70	08	26.66
Diagnosed with Diabetes since (years):		
1-5	14	46.70
6-10	13	43.30
>11	03	10.00

Details of comorbidities in participants

Table 2: Details of comorbidities in participants.

Co-morbidities	Frequency	Percentage
Hypertension	15	50.00
Hypothyroidism	01	03.30
Dyslipidemia	02	06.70

Details of Medication information in participants: In the study, 4(13.3%) patients were on metformin monotherapy, 14(46.6%) were using Metformin + Glimepiride combination, 9(30%) were using combination of Metformin + Glimepiride + Voglibose. 3 (10%) patients were using various other combinations.

Table 3: Details of Medication information in participants.

Medication*	Frequency	Percentage
Metformin (Monotherapy)	04	13.3
Metformin + Glimepiride	14	46.6
Metformin + Glimepiride + Voglibose	09	30.0
Others	03	10.0

Details of ADRS in participants

Table 4 was used to compare the adverse drug reactions (ADRs) experienced by branded and generic users. Statistical analysis was performed and a P value was obtained. The obtained P values were not statistically significant.

Table 4: Details of ADRS in participants.

ADRs	Branded Frequency and (%)	Generic Frequency and (%)	Test Statistics	P Value
Diarrhoea	09 (52.9)	08 (47.1)	0.136	0.713
Dizziness	02 (28.6)	05 (71.4)	1.721	0.390
Pain or Numbness in knees and joints	05 (41.7)	07 (58.3)	0.556	0.456
Acidity or Sour stomach	06 (46.2)	07 (53.8)	0.556	0.456
Light headedness and tiredness	03 (75.0)	01 (25.0)	1.154	0.598

***p value <0.05 is considered statistically significant**

Analysis of RBS and HbA1c parameters in participants

Table 5 and 6 show the comparison of RBS and HbA1c values in branded and generic metformin users. Branded metformin showed a slightly better action in RBS levels, with a mean difference of 63.53, and the difference was statistically significant. Comparing HbA1c values, branded users showed a mean difference of 0.766, whereas generic users showed difference of 0.4, P values of their difference was not statistically significant implying that the action of both branded and generic metformin was same in HbA1c levels.

Table 5: Analysis of RBS and HbA1c parameters in Generic drug group.

Study variables	Generic drug group		Mean difference	Test statistics	P value
	Baseline	Follow up			
RBS mg/dl	252.00±58.33	202.27±61.780	49.733	5.333	**0.0001***
HbA1c %	8.86 ±1.124	8.46±1.125	0.400	3.055	0.19*

***p value <0.05 is considered statistically significant**

Table 6: Analysis of RBS and HbA1c parameters in Branded drug group.

Study variables	Branded drug group		Mean difference	Test statistics	P value
	Baseline	Follow up			
RBS mg/dl	239.80 ± 91.22	176.27 ±57.43	63.53	3.526	**0.003***
HbA1c %	8.77 ±2.41	8.00 ±1.94	0.766	2.596	0.21*

***p value <0.05 is considered statistically significant**

Details of management of diabetic symptoms in participants

Patients were asked if their health has improved and if they are able to manage their symptoms in a better way, 93.33% Branded users said yes and 6.66% persons said no. As compared to 86.66% Generic users that said yes and 13.33% that said No. This data is shown in a comparative bar graph in Figure 1.

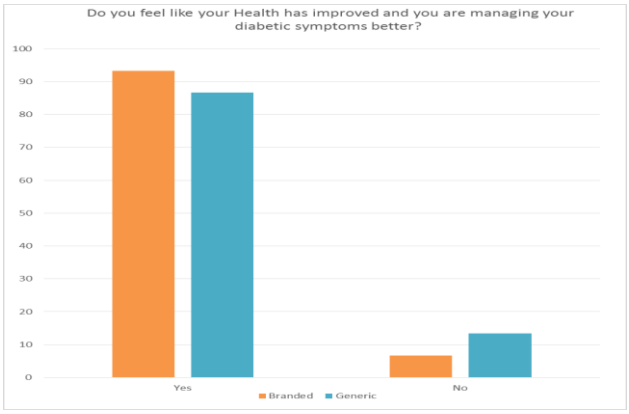

Figure 1: Details of management of diabetic symptoms in participants.

Details of user preference towards branded metformin

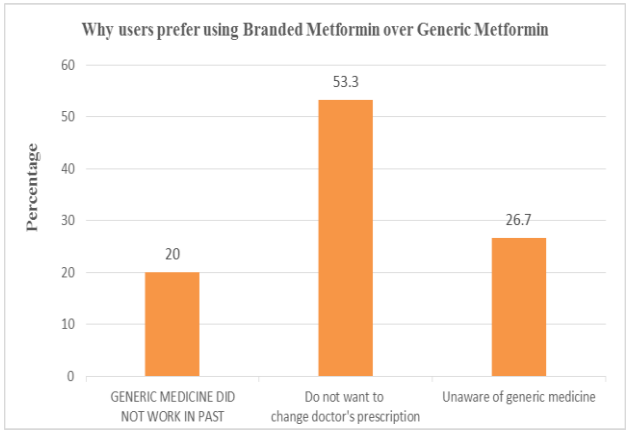

Figure 3: User preference towards branded medicine over generic medicine.

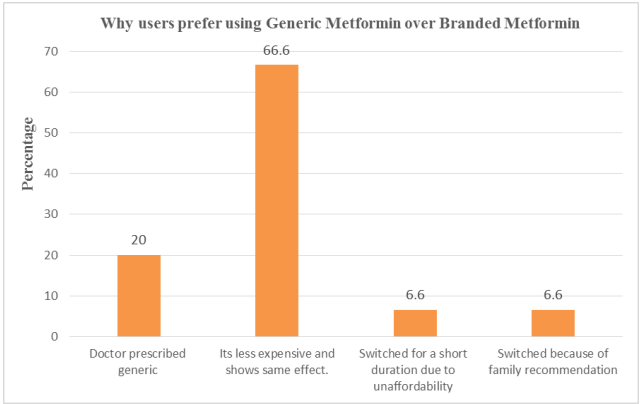

Figure 4: User preference towards generic medicine over branded medicine.

DISCUSSION

This study collected data from 30 patients over a period of three months, with 15 using branded metformin and 15 using generic metformin. The study focused on the safety, efficacy, and quality of life of metformin users, and the data collection form was designed to cover both clinical and humanistic outcomes. The form included 26 questions about patient

demographics, medication and refill information, ADRs, RBS and HbA1c values, quality of life, and patient perception towards generic and branded medicine. Due to limitations in the data pool, the study may not be fully representative of the population, but complete data from willing participants was compiled to obtain results and conclusions.

Safety of metformin by comparison of ADRs seen in enrolled patients

Safety of metformin was calculated by observing number of ADRs in each participant. These ADRs were further classified and compared between generic and branded metformin. The most common ADR reported in participants was diarrhea (56.7%), followed by acidity and sour stomach (43.3%), and pain or numbness in knees and joints (40%). Differences in ADRs between branded and generic metformin users were not statistically significant, indicating that both are equally safe. The least common ADR was light headedness and tiredness (13.3%).

Evaluation of efficacy of metformin by comparing clinical end points

The efficacy of branded and generic metformin was evaluated by comparing the clinical endpoints of RBS and HbA1c. These parameters were chosen as they are specific to Diabetes Mellitus and HbA1c reduction is a validated surrogate endpoint for reducing microvascular complications associated with diabetes mellitus. Due to time constraints, only RBS and HbA1c were selected instead of FBS and PPBS. Previous studies such as those conducted by Akina Hori et al and the National Institutes of Health have also utilized these parameters in evaluating the efficacy of metformin.

The study evaluated the efficacy of branded and generic metformin by comparing the decrease in RBS and HbA1c over a period of three months. Branded metformin showed better action in decreasing RBS levels, with a mean difference of 63.53 compared to 49.73 for generic metformin. However, there was no significant difference in the decrease of HbA1c levels between the two groups. The p values obtained were 0.003 and 0.0001 for RBS, and 0.21 and 0.19 for HbA1c, respectively.

CONCLUSION

The study found no significant difference in safety between branded and generic metformin in enrolled participants, and concluded that both were equivalent in terms of safety.

In terms of efficacy, branded metformin showed slightly better action on RBS levels compared to generic metformin, while there was no significant difference between the two in terms of HbA1c levels. Overall, the study suggests that branded and generic metformin are comparable in terms of safety and efficacy.

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