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ORIGINAL ARTICLE **OPEN ACCESS**

Evaluation of Adverse Drug Reactions among Diabetes Patients Treated With Antidiabetic Drug in Tertiary Care Teaching Hospitals

Lalendra Yadav[1*], Jyotsna Sharma[2], Shaktibala Dutta[3], Ila Pahwa[4], Amit Kumar[5]
[1,2,3,5] Department of of Pharmacology, Santosh Medical college & Hospital, Santosh Deemed to be University, Ghaziabad, UP
[4] Department of Medicine, Muzaffarnagar Medical College, Muzaffarnagar, Chaudhari Charan Singh University, Meerut, UP
Email: yadavlalendra@gmail.com

ABSTRACT
Diabetes mellitus is a chronic metabolic disorder caused by deficiency (inherited and/or acquired) of insulin production or by the development of insulin resistance that can be controlled by various types of newer or concurrent drugs which may lead to the occurrence of ADRs along with therapeutic responses with the aim of evaluation of ADRs in DM patients treated with Antidiabetic drugs. This was a prospective and observational study conducted in the Department of Pharmacology, Santosh Medical College and Hospital, Ghaziabad in Collaboration with the Department of Medicine, Muzaffarnagar Medical College, Muzaffarnagar. Total 100 patients of DM treated with Antidiabetic drugs and visited in OPD of Medicine, Muzaffarnagar Medical College were taken of whose ADRs were recorded and evaluated with the help of ADRs form uploaded by CDSCO-PvPI. The prevalence of ADRs was 20%(20/100) and Biguanide was the drug that exaggerated the maximum number of ADRs 30% predominantly in female patients 65%, those were reduced by the combination of various groups of antidiabetic drugs.4. ADRs exaggerated by Antidiabetic drugs were reduced by drug combinations of various groups of Antidiabetic drugs.
KEYWORDS: *Diabetes mellitus, Antidiabetic drugs, ADRs, WHO-UMC, Naranjo's causality assessment scale.*

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INTRODUCTION

Diabetes mellitus is a chronic disease caused by deficiency (inherited and/or acquired) of insulin production or by the development of insulin resistance. This deficiency leads to increased blood glucose concentrations that cause damages to various bodies' systems, particularly the blood vessels and nerves. Worldwide Diabetes mellitus is moderately increasing globally and about to reach an epidemic ratio in many countries [1-2]. The current data shows that 351.7 million people of working age (20–64 years) with diagnosed or undiagnosed diabetes in 2019 which is expected to increase to 417.3 million by 2030 and to 486.1 million by 2045. The maximum number will take place in regions where economies are moving from low- to middle-income status [3]. India has the second-largest diabetic population in the world. In 2015, about 60 million people in India are suffering from diabetes. Moreover, 75 million people are at the risk to develop diabetes and more than 65.1 million individuals have been diagnosed with the disease and the estimates suggest that 89 million patients may develop by 2030 [4].Simultaneously the advent of newer drugs, the evolution of science, and the number of treatment options for a single disease have increased. But as every drug has it's a benefit as well as side effects. Therefore every drug in the therapeutic area poses both benefits as well as is a potential threat for causing severe side effects. At times, these side effects are preventable, and timely reporting of the same can avoid unwanted health hazards and save millions of people. Thus an initiative was made in the direction of same and was to design and implement adverse event reporting systems by individual nations and then were adopted by the whole world either collaboration with global organizations or individualizing their reporting system [5].

As we know that few effects of the drug are elicited only once the drug has been administered to a larger population for a longer duration of time. The adverse drug reaction or event reporting from such a huge population would be possible only after active involvement of the researchers and voluntary reporting

from the peripheries and tertiary care was done extensively. Pharmacovigilance of anti-diabetic drugs can play an important role in detecting adverse drug reactions (ADRs) and providing feedback to physicians on the possibility and details of such events, thereby protecting the patients from that avoidable harm and ADRs. In India, Pharmacovigilance activities are still in a little stage in comparison to providing the total demand of the drugs to a global market, so initiatives are being taken for spontaneous ADRs reporting under the Pharmacovigilance Programme of India (PvPI) [6]. Therefore the present study has been undertaken for the evaluation of adverse drug reactions among diabetes patients treated with Antidiabetic drugs in tertiary care teaching hospitals.

MATERIAL AND METHODS

Study Design and Place

It was a prospective and observational study for the evaluation of adverse drug reactions (ADRs) among diabetes patients treated with Antidiabetic drugs in tertiary care teaching hospitals from October 2018 to October 2020**.** This study was carried out in the Department of Pharmacology Santosh Medical College and Hospital in collaboration with the Department of Medicine, Muzaffarnagar Medical College, Muzaffarnagar, Uttarpradesh. This study was a part of our PhD research work and was started only after the approval of the Institutional ethics committee.

Study Population:-

Total 100 patients of diabetes mellitus (DM) of age group above 18 Years and of both sexes (male and female) treated with Antidiabetic drugs were taken.

METHODOLOGY:

The various study tools that have been used were the Suspected Adverse Drug Reaction Reporting Form issued by the Central Drugs Standard Control Organization (CDSCO) under the Pharmacovigilance Programme of India (PvPI) version 2.0, that was recorded all the information, relevant history, including pre-existing medical conditions, details of suspected adverse drug reactions and details of suspected medications that the patients might be taken. ADRs reporting form was recorded all the essential information regarding the adverse effects: the onset and severity of the ADRs experienced the impact of ADRs on the treatment and worked capacity of the patient, the drug(s) involved, the date of starting the suspected drugs and the date of reporting of the ADRs. Causality assessment was done using UMC- WHO causality assessment scale and Naranjo's causality assessment scale [7-8]. Our study included Diabetes patients of both Type-I DM and Type-II DM and both sexes (Male & Female), old patients as well as newly diagnosed patients of DM and treated with any antidiabetic drugs with age group above 18 years. The study also excluded the patients who were associated with any other comorbid conditions, wasn't willing to participate and gave their consent and pregnant and lactating mothers.

Statistical Analysis

Demographic variables were presented in number and percentage (%). Statistical analysis was performed using Graph Pad software available online at http://graphpad.com/quickcalcs/. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 16.0.

RESULT AND DISCUSSION

The present study showed that there was a total of 100 patients of either type I DM (6%) and type II DM (94%) screened in the study during the study period among them the maximum number of patients was a female type (56%) followed by male (44%) patients, out of them the prevalence of ADRs were larger in female patients 55% (11) than in male patients 45% (9) which was opposite to the study done by Mamta *et al* [9] found to be 54% ADRs in males patients followed by 46% in females patients, that difference was perhaps due to the place variations and depicted in fig 1.

A study also showed that the ages of the patent were divided into six groups among them a maximum number of patients belonging to age group 40-50 years (35), followed by age group 51-61 years (33), 29-39 years (13), 62-72 years (12), 73-83 years (6) and 18-28 years (5) and which were similar to study done by Mamta et al [9] found highest in 41-60 years (54%) followed by 61-80 years (28%) and depicted in Fig 2 which indicated that occurrence of ADRs depends on the age of patients Fig 3; shown that the types of ADRs which was occurred after starting the drug therapy in DM patients which shown that out of 100 patients 20 (20%) patients shown 17 types of ADRs in which larger number of people suffer with abdominal pain 25% (5) followed by acidity 20% (4), weakness 20% (4), nausea 15% (3), constipation 10% (2), headache 10% (2), loss of appetite 10% (2), alteration in taste 5% (1), numbness 5% (1), tingling sensation 5% (1), GI upset 5% (1), mouth ulcer 5% (1), vomiting 5% (1), wt. loss 5% (1), giddiness 5% (1), itching 5% (1) and rashes 5% (1).

Table 1, showing that the number and percentages of patients who were prescribed by various drug and drugs combinations, the number and percentage of patients who showed ADRs by those particular groups of drugs and types of ADRs that occurred by that particular group of Drugs. The analysis of drugs showed that the maximum number of drugs prescribed in the diabetic patients belong to group Biguanides + sulfonylureas 43% (43) followed by Biguanide alone 31% (31), Biguanide + sulphonylureas + Thiozolidinedione 8% (8) Biguanide + DPP4-inhibitors 6% (6), Alphaglycosidase inhibitors 6% (6) and insulin derivatives 6% [6]. The prevalence of ADRs in our study was encountered to be 20% (20/100) while a study was done by Mamta *et al*; 33.33% and Singh and Dwivedi showed 11.8% [10]. The maximum ADRs occurred in drugs group Biguanides + sulfonylureas 50% (10/20) followed by Biguanide alone 30% (6/20), Alphaglycosidase inhibitors 5% (1/20), Biguanide + DPP4-inhibitors 5% (1/20) and Insulin derivative 5% (1/20). The ADRs percentage was found to be the highest (50%) in patients receiving both Sulphonylureas and Biguanide. This combination might reflect the usage of multiple drugs to treat concurrent complications in diabetic patients. Further analysis of specific types of drugs showed that metformin was the majority prescribed drug 88% as monotherapy 31% and as a combination therapy 57%. Among OHAs metformin alone contributed 30% of ADRs while a study conducted by Mamta et al; it as 23.72% and Sheehan reported it as 30% were in the main side effect of metformin reported as gastrointestinal disturbances (Headache, Weakness, Giddiness, Abdominal pain, nausea, acidity) [11]. The study also showed that when metformin is combined with others OHAs like Tenegliptine, Pioglitazone and Glimepiride then it reduces the occurrence of ADRs (5%>5% >25% >30%) respectively. Thus combination therapy of metformin drug is more important for treating Diabetes mellitus patients than monotherapy. Evaluation and causality assessment of ADRs using UMC-WHO and Naranjo's scales showed 13% and 5% as possible and probable respectively (Fig. 5 & 6), all the reactions were predictable types the severity scale showed that majority of ADRs were found to be mild 67% (14) followed by moderate 33% (6) and no any severe reaction was reported (Fig.7) by Modified Hartwig and Siegel scale. The Preventability scale showed that the reactions were categorized as definitely preventable (65%), probably preventable (35%) by using the Modified Schumock and Thornton Scale (Fig.8) and no ADRs were found to be fatal.

Fig 1.Gender wise distribution of Patients

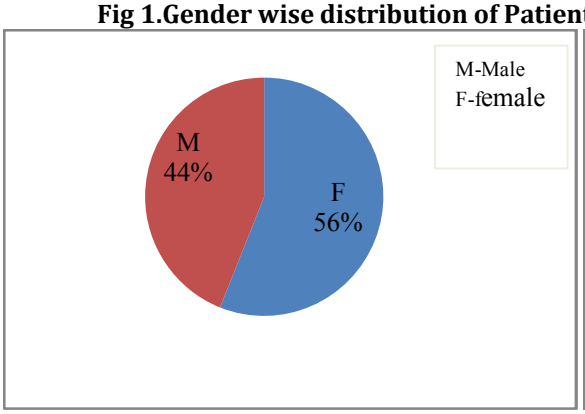

Fig 2. Age wise distribution of Pts

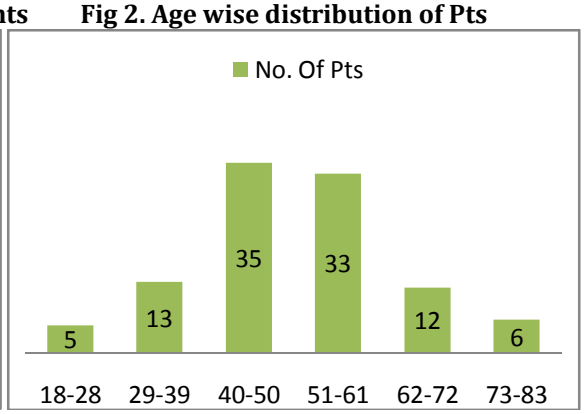

Fig 3.Types of ADRs

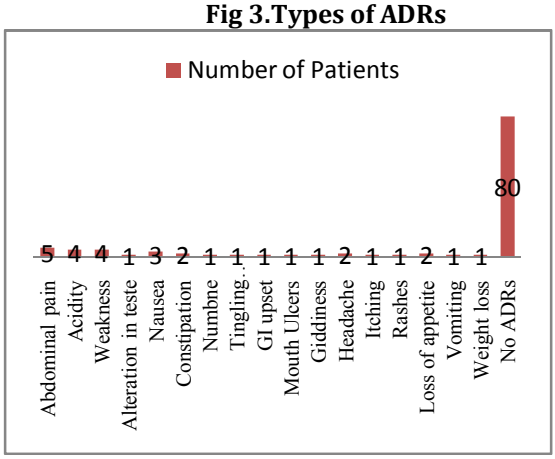

Fig. 4. **Types of Drugs prescribed**

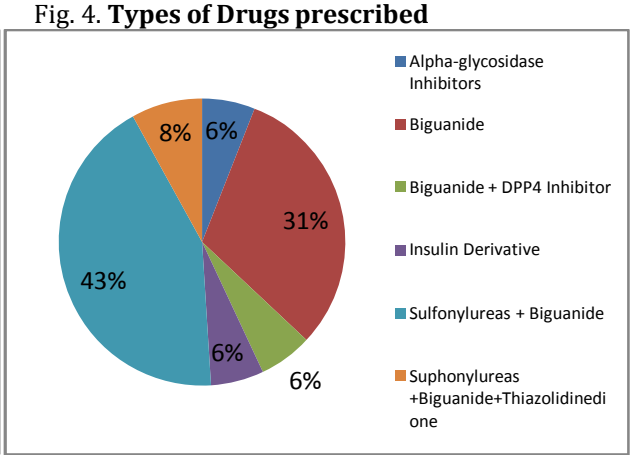

Fig 5. UMC-WHO Causality Assessment Scale

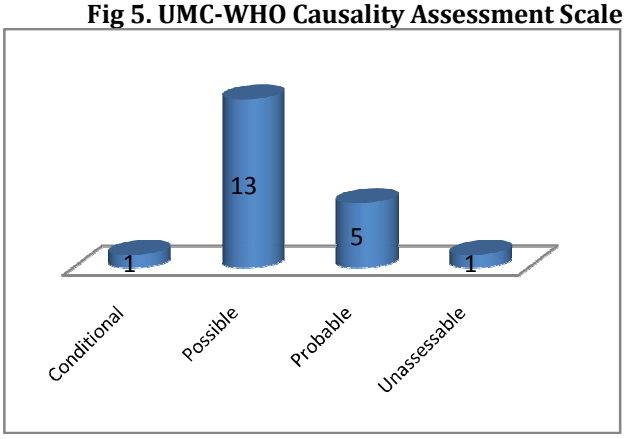

Fig 6. Naranjo's Causality Assessment

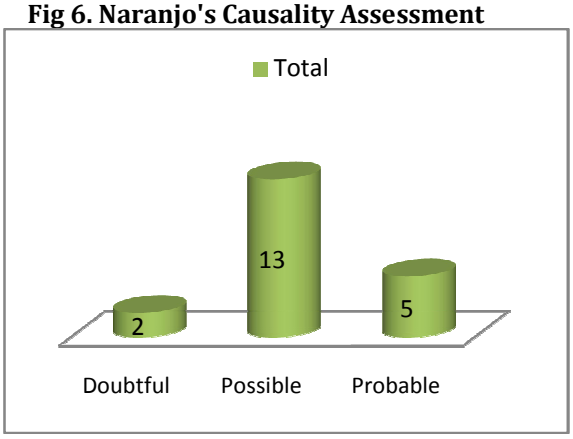

Fig 7. Siegel scale

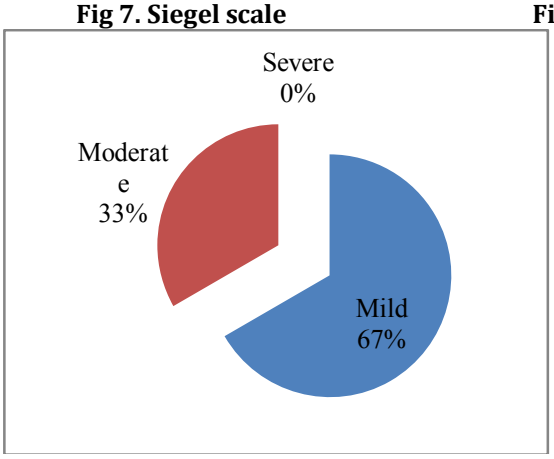

Fig 8. Modified Schumock and Thornton Scale

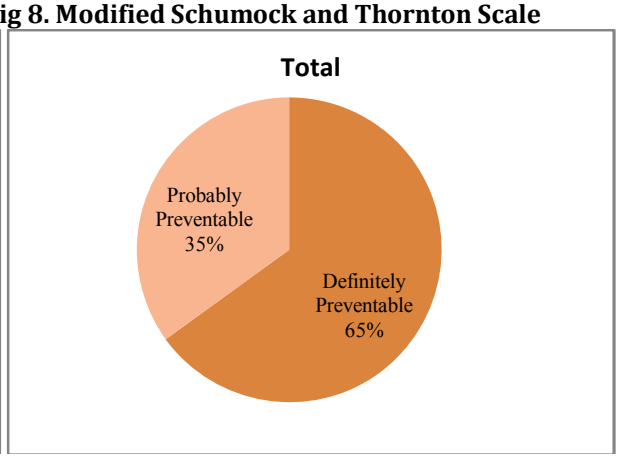

Table-1 Percentages of patients prescribed by various drug and drugs combinations

Name of the drugs causing ADRs	Total No. of pts. prescribed	% of total prescription	No. of pts causing ADRs	% of ADRs	Types of ADRs
Glimepiride 1mg + Metformin 500mg	29	29%	5	25%	Acidity, abdominal pain, loss of appetite, constipation.
Glimepiride 2mg + Metformin 500mg	14	14%	5	25%	Weakness, Wt. loss, alteration in taste, nausea, constipation, numbness, tingling sensation, acidity
Glimepiride 2mg + Metformin 500mg+Pioglitazone 15mg	8	8%	1	5%	Abdominal pain
Insulin isophan/NPH 70% +Human insulin/soluble insulin 30%	6	6%	1	5%	Itching, Rashes
Metfomin 500mg + Teneligliptin 20mg	6	6%	1	5%	GI upset, Mouth ulcer, vomiting, loss of appetite,
Metformin 1000mg	7	7%	2	10%	Headache, Weakness,
Metformin 500mg	24	24%	4	20%	Abdominal pain, Giddiness, nausea, acidity,
Voglibose 0.3mg	6	6	1	5%	Abdominal pain,

CONCLUSION

A metabolic disorder like Diabetes mellitus requires long term treatment with anti-diabetic drugs with or without insulin along with lifestyle modification to prevent life-threatening complications. The selection of anti-diabetic therapy depends on the type and severity of the disease. In the present study setting a greater number of patients received biguanide OHAs and it showed more ADRs in comparison to other groups of OHAs but those ADRs were controlled by the combination therapy of biguanide with other OHAs that gave the key of the drug combination in the therapy of such chronic metabolic diseases.

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