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ADVERSE DRUG REACTION MONITORING AMONGST DIABETIC PATIENTS OF TERTIARY CARE CENTRE OF NORTHERN INDIA RELATED TO ANTI-DIABETIC DRUGS

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ABSTRACT: Diabetes mellitus caused by inherited and/or acquired deficiency in insulin production or by the development of insulin resistance. This is chronic as well as moderately increasing day by day in developing countries as well as globally and has reached about to the epidemic ratio, and now it is a matter of worry for the populations. This deficiency results in increased blood glucose concentrations, which damages many of the body's systems, in particular the blood vessels and nerves. There are several medications available for the disease. Worldwide, different drugs are prescribed in different manners as well as amount, which may cause severe side effects known as adverse drug reactions (ADRs). So, ADR monitoring is being an important task to reduce the damage by the drugs taken for the disease treatment. This study was performed for the ADRs monitoring of anti-diabetic medication in OPD of tertiary care hospital of northern India.

INTRODUCTION: Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in insulin production or by the development of insulin resistance. This deficiency results in increased blood glucose concentrations, which damages many of the body's systems, in particular the blood vessels and nerves. Diabetes mellitus is moderately increasing globally and about to reach an epidemic ratio in many countries worldwide [1, 2].

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Recently compiled data show that approximately 150 million people have diabetes mellitus worldwide and that this number may well double by the year 2025. Much of this increase will occur in developing countries and will be due to population growth, aging, unhealthy diets, obesity, and sedentary lifestyles. By 2025, while most people with diabetes in developed countries will be aged 65 years or more, in developing countries, most will be in the 45-64year age bracket and affected in their most productive years [2, 3].

Same time with the advent of newer medicines and the evolution of science, the number of treatment options for a single disease has increased. But as every drug has its benefits 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 a timely reporting of the same can avoid unwanted health hazards and save millions of lives. An initiative made in the same direction was to design and implement adverse event reporting systems by individual nations and then were adopted by the whole world either unanimously with global organizations or individualizing their own reporting system. Diabetes currently affects more than 62 million Indians, which is more than 7.1% of the adult population [4]. The average age on onset is 42.5 years. Nearly 1 million Indians die due to diabetes every year [5]. According to the Indian Heart Association, India is projected to be home to 109 million individuals with diabetes by 20356. A study by the American Diabetes Association reports that India will see the greatest increase in people diagnosed with diabetes by 20307. The high incidence is attributed to a combination of genetic susceptibility plus adoption of a high-calorie, low-activity lifestyle by India's growing middle class [8].

Certain effects of the drug are elicited only once the drug has been administered to a larger population for a larger duration of time. The adverse drug reaction or event reporting from such big population would be possible only after active involvement of the researchers and voluntary reporting from the peripheries were done extensively [9]. This is when the systems like and prescription event monitoring and pharmaco-vigilance were developed. Prescription event monitoring differs from pharmacovigilance in the aspect that it is a more centralized and unbiased approach to report responses from a medicine's use than other approaches that are centered only on reporting the adverse events. Therefore this study has been undertaken for ADR monitoring of anti-diabetic drugs prescribed in OPD of tertiary care hospital of northern India.

MATERIALS AND METHODS: It is a prospective observational study of adverse drug reaction monitoring to drugs used for diabetes mellitus type-2 treatment. This study was carried out on the patients at the Department of Medicine Rama Medical College, Kanpur. The duration of the study was 6 months. The study started only after the approval of the Institutional ethics committee. The various study tools that will be used are the Suspected Adverse Drug Reaction Reporting Form issued by the Central Drugs Standard Control Organization (CDSCO) under the Pharmacovigilance Programme of India (PvPI), which will record 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 taking. ADR Reporting Form records all the essential information regarding the adverse effects: the onset and severity of the ADR experienced, the impact of ADR on the treatment and work capacity of the patient, the drug(s) involved, the date of starting the suspected drugs and the date of reporting of the ADR. Causality assessment will be done using Naranjo's causality assessment scale [10].

Data Management and Analysis: Data will be aggregated according to disease profile and other relevant information required for the study. Causality assessment was done using Naranjo's causality assessment scale [11].

Inclusion Criteria:

- Newly diagnosed patients of diabetes mellitus type-2.
- Patients with age more than 18 years.
- Patients of either sex.
- Patients have a baseline (pre-treatment) biochemical parameters other than blood sugar (*i.e.,* liver function test, kidney function test) within the normal range.
- Patients have no associated comorbidities.

Exclusion Criteria:

- Patients who were unwilling to participate and did not give consent in the study.
- Patients who were unable to give an interview.
- Patients with incomplete medical records.
- Patients with chronic liver disease such as cirrhosis, chronic hepatitis, and acute viral hepatitis.
- Terminally ill patients.

- Patients with concurrent major psychiatric illness and/or concurrent major medical illnesses.

Statistical Analysis: Categorical variables were presented in number and percentage (%). Qualitative variables were compared using Chi-Square test /Fisher's exact test as appropriate. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using GraphPadQuickCalcs 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 21.0.

RESULT: The present study was open and non-comparative, based on a questionnaire (ADR monitoring form) drafted according to Naranjo ADR monitoring guidelines., which included past medical history, present drug treatment, description, assessment and treatment of ADR. The study protocol was approved by the Institutional medical ethics committee, Rama Medical College & research center, Kanpur, U. P. Present study was conducted between 1- 06- 2018 to 30-11-2018by attending the medicine OPD on a daily basis. A total of 16 ADRs were observed in 120 patients during the study.

Adverse Drug Reactions (ADRs): Out of 120 patients, 16(13.33%) ADRs were recorded. Maximum ADRs about 43.75% (7 ADRs) were seen in elderly patients (> 60 yr), 25% (4 ADRs) in the age group between 60 and 51yr, 18.75% (3 ADRs) between 50 and 41 yr and 12.5% (2 ADRs) between 31 and 40 yr **Fig. 1**. Among 55 patients on monotherapy, 7 ADRs were observed; however, in 65 patients on combination therapy, 9 ADRs were recorded. Among 16 patients, who had ADR, 10 patients were male, and 6 were female. Percentage-wise ADR occurrence among all male patients was14.70%, and in female patients, it was 11.53% **Fig. 2**.

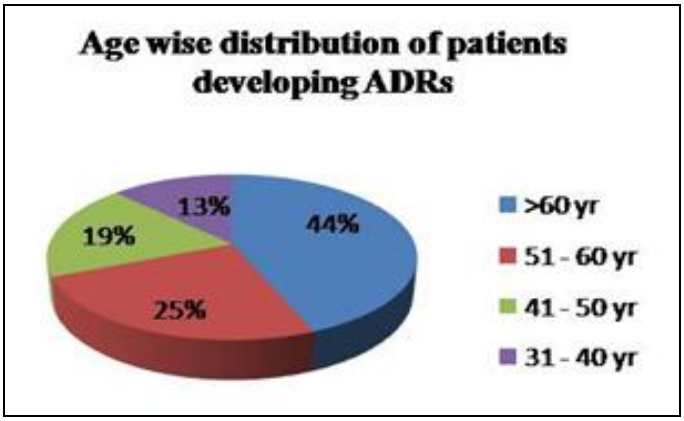

FIG. 1: THE PIE GRAPH SHOWS THE DISTRIBUTION OF TYPE II DIABETES PATIENTS BASED ON DRUG PRESCRIPTION PATTERN, WHERE 100% IS THE TOTAL NUMBER OF PATIENTS' POPULATION (N=120)

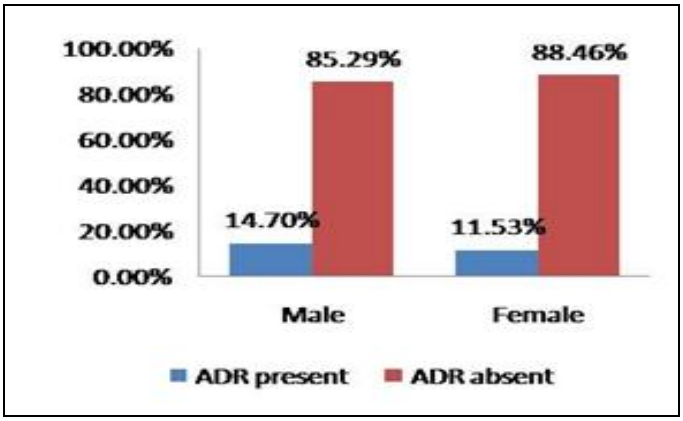

FIG. 2: THE BAR GRAPH SHOWS THE % FREQUENCY OF ADR IN TYPE II DIABETES PATIENTS BASED ON GENDER WHERE 100% IS THE TOTAL NUMBER OF PATIENTS' POPULATION (N=120)

Out of 16 ADRs recorded, 12.5% (5 out of 40) was observed in patients prescribed Metformin alone, 13.33% (2 out of 15) in patients prescribed Glimipride/Gliclazide alone, in combination therapy, 11.11% (6 out of 36) with Metformin plus Glimipride/Gliclazide, 10% (1 out of 10) with Metformin plus Glimipride/Gliclazide plus Glitazone, 10.52% (2 out of 16) with Metformin plus Dipeptidyl-transferase IV inhibitor **Fig. 3**.

Total of 16 (13.33%) adverse drug reactions were observed **Fig. 4**. Following adverse drug reactions were observed, which have been categorized as per System of Organ Class (SOC):

Gastrointestinal-related adverse drug reactions (dyspepsia, diarrhoea, vomiting, Gastric irritation) contributed 7/16(43.75%) to the total ADRs developed. While incidence of dyspepsia was 3/16 (18.75%), diarrhea 1/16(6.25%), vomiting 1/16 (6.25%), gastric irritation was 2(12.5%). Metabolic Disorders related adverse drug reaction (hypo-glycemia) contributed 3/16 (18.75%) to the total ADRs developed. Skin and Appendages related

adverse drug reaction (allergic reaction) contributed 2/16(12.5%) to the total ADRs developed. Musculoskeletal System related adverse drug reactions contributed 2/16(12.5%) to the total ADRs developed.

Central Nervous System related adverse drug reaction (dizziness) contributed 1/16(6.25) to the total ADRs developed. Respiratory System related adverse drug reaction (nasopharyngitis) contributed to 1/16(6.25) the total ADRs developed.

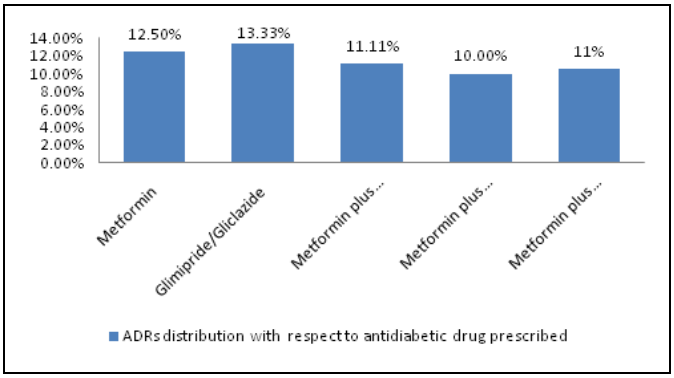

FIG. 3: THE BAR GRAPH SHOWS THE % FREQUENCY OF ADR DISTRIBUTION WITH RESPECT TO ANTI-DIABETIC DRUG PRESCRIBED IN TYPE II DIABETES PATIENTS WHERE 100% IS THE TOTAL NUMBER OF PATIENTS POPULATION (N=120)

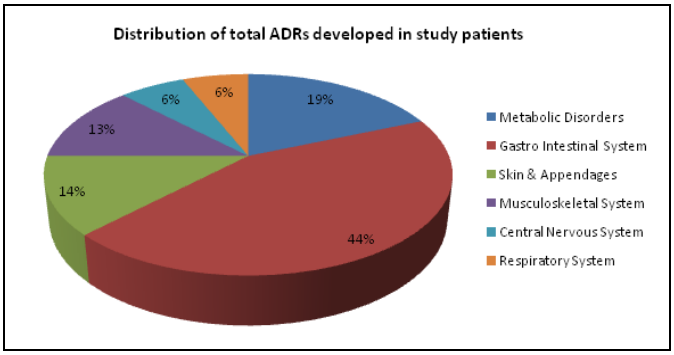

FIG. 4: THE PIE GRAPH SHOWS THE DISTRIBUTION OF TOTAL ADRS DEVELOPED IN TYPE II DIABETES PATIENTS WHERE 100% IS THE TOTAL NUMBER OF PATIENTS POPULATION (N=120)

ADR Due to Oral Antidiabetic Monotherapy:

Metformin: 31.25% (5 out of 16) adverse drug reaction of the total ADRs developed due to metformin monotherapy. All of these were related to Gastrointestinal system (dyspepsia contributed to 18.75%, diarrhoea contributed to 6.25% and vomiting contributed to 6.25% of total ADRs).

Glimipride/Gliclazide: 12.5% (2 out of 16) adverse drug reaction of the total ADRs developed due to Glimipride/Gliclazide monotherapy. These were related to Metabolic disorders (Hpoglycemia contributed to 12.5% of total ADRs).

ADR Due to Oral Antidiabetic Combination Therapy:

Metformin plus Glimipride/Gliclazide: 37.5% (6 out of 16) adverse drug reaction of the total ADRs developed due to Metformin plus Glimipride / Gliclazide combination therapy. 6.25% (1 out of 16) were related to Metabolic disorders (hypoglycaemia contributed to 6.25%). 12.5% (2 out of 16) were related to Gastrointestinal System (gastric irritation contributed to 12.5%). 6.25% (1 out of 16) were related to Skin and appendages (allergic reactions contributed to 6.25%) . 6.25% (1 out of 16) were related to Musculoskeletal system to myalgia contributed to 6.25%). 6.25% (1 out of 16) were related to the Central nervous system (dizziness contributed to 6.25%).

Metformin Plus Glimipride/Gliclazide Plus Glitazone: 6.25% (1 out of 16) adverse drug reaction of the total ADRs developed due to Metformin plus Glimipride/Gliclazide plus Glitazone combination therapy. These were related to the Musculoskeletal system (myalgia contributed to 6.25%).

Metformin Plus Dipeptidyltransferase IV Inhibitor: 12.5% (2 out of 16) adverse drug reaction of the total ADRs developed due to Metformin plus Dipeptidyltransferase IV inhibitor combination therapy. 6.25% (1 out of 16) were related to Skin and appendages (allergic reaction contributed to 6.25%). 6.25% (1 out of 16) were related to Musculoskeletal system (myalgia contributed to 6.25%) **Fig. 5**.

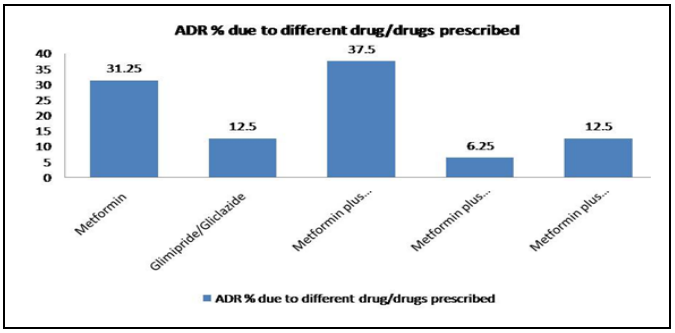

FIG. 5: THE BAR GRAPH SHOWS THE % FREQUENCY OF ADR DISTRIBUTION IN TYPE II DIABETES PATIENTS BASED ON ANTIDIABETIC DRUG /DRUGS PRESCRIBED WHERE 100% IS THE TOTAL NUMBER OF PATIENTS POPULATION (N=120)

Causality of the Adverse Drug Reactions: The causality assessments of ADRs was done according to Naranjo scale which categorises ADRs as "definite", "probable", "possible" and "doubtful". As per Naranjo's Algorithm almost 31.25% of the ADRs were categorized as "probable" with score ranging from 5-8, 62.5% of the ADRs were categorized as "possible" with score ranging from 1-4, 6.25% of the ADRs were categorized as "doubtful" with score <1 **Fig. 6**.

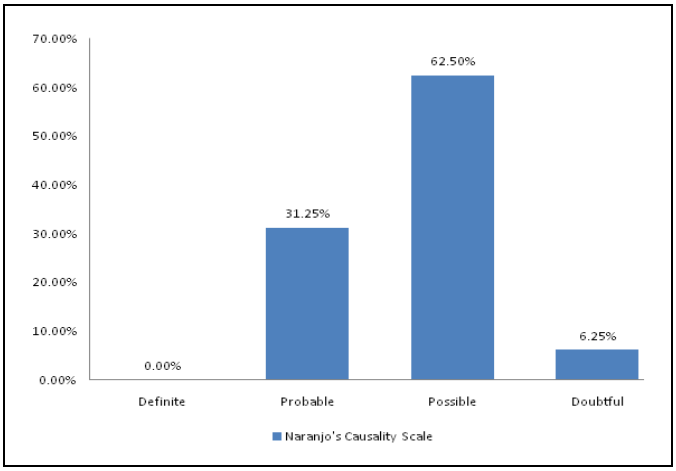

FIG. 6: THE BAR GRAPH SHOWS THE % FREQUENCY OF ADR IN TYPE II DIABETES PATIENTS BASED ON NARANJO'S CAUSALITY SCALE WHERE 100% IS THE TOTAL NUMBER OF PATIENTS POPULATION (N=120)

From the above illustration of data on incidence and pattern of adverse drug reactions, 13.33% of ADRs were observed in 120 study patients of type II diabetes being treated on oral antidiabetic medication, were found in agreement with previous reports from similar studies [12-15].

Discussion: A total of 120 patients with type II Diabetes mellitus were monitored for adverse drug reaction in this six months period of study.

Demographic and Health Characteristics: The total number of males in the study was 68(56.7%) while females were 52(43.3%).This is in agreement with previous reports as shown in a study by Singh *et al.,* [16], who included 55% of males while 45% were females, a similar study by Saravanan *et al.,* [17] included 60% males rest 40% of females, another study included 51% males while 49% were females. Age-wise distribution of patients showed 6(5%) were aged between 21-30 Yrs, 13(10.8%) between 31-40 Yrs, 35(29.2%) between 41-50 Yrs, 45(37.5%) between 51-60 Yrs, 18(15%) between 61-70 Yrs and 3(2.5%) in >70 Yrs. It was observed from age-wise distribution that the maximum no. of patients with diabetes 37.5% were aged between 51 – 60 Yrs and then 29.2% between 41 – 50 Yrs. This was found in agreement with a study done, which showed almost similar observations, maximum no. of patients with diabetes 37% were between 51 – 60 Yrs, and 26% were between 41 – 50 Yrs [16]. Duration of diabetes was between 16 and 20 Yrs in 12(10%) patients, 11-15 Yrs in 21(17.5%) patients, 6-10 Yrs in 36(30%) patients, and ≤5 Yrs in 51(42.5%) patients. It was found that the maximum no. of patients, 42.5% had ≤5 Yrs duration of diabetes. Similar pattern was seen in a study done by Singh *et al.,* [16] where 43.6% of patients had ≤5 Yrs duration of diabetes. In contrast studies showed 29.5% of patients had ≤5 Yrs duration of diabetes whereas a maximum no. of patients 36.5% were in the timeframe of 5 – 10 Yrs duration of diabetes.

Adverse Drug Reactions (ADRs): We studied 120 patients on oral antidiabetic medications and observed the pattern of adverse drug reactions in them. Out of 120 patients, 16 (13.33%) ADRs were recorded. On similar lines, a study done by Singh *et al.,* recorded 11.8% of ADR16. A study recorded 27.6% ADR in their study. Few studies showed a higher percent of ADR, too as seen in a study done by Saravanan *et al.,* which recorded 46.7% ADR [17]. Maximum ADRs about 43.75% (7 ADRs) were seen in elderly patients (>60 Yrs), 25% (4 ADRs) in the age group between 60 and 51 Yrs, 18.75% (3 ADRs) between 50 and 41 Yrs and 12.5%(2 ADRs) between 31 and 40 Yrs. Singh *et al.,* also observed maximum ADRs of about 42.31% in elderly patients (>60 Yrs). Similarly, studies found the incidence of ADR 1.23 times higher in patients who were aged more than 65 years of age.

Among 55 patients on monotherapy, 7 ADRs were observed; however, in 65 patients on combination therapy, 9 ADRs were recorded. Among 16 patients, who had ADR, 10 patients were male, and 6 were female. Percentage-wise ADR occurrence among all male patients was 14.70%, and in female patients, it was 11.53%. This is in agreement with previous reports as seen in a study done by Saravanan *et al.,* [17,] who found 77.14% ADR in males and 22.86% in females. Similar findings were observed by Singh *et al.,* [16] with percentage occurrence of ADR 61.53 in males and 38.46% in females. Out of 16 ADRs recorded, 12.5% (5 out of

40) was observed in patients prescribed Metformin alone, 13.33% (2 out of 15) in patients prescribed Glimipride/Gliclazide alone, in combination therapy, 11.11%(6 out of 36) with Metformin plus Glimipride/Gliclazide, 10%(1 out of 10) with Metformin plus Glimipride/Gliclazide plus Glitazone, 10.52% (2 out of 16) with Metformin plus Dipeptidyltransferase IV inhibitor. In our study it was found that Glimipride / Gliclazide is responsible for causing maximum ADR followed Metformin in their users. On similar lines recorded 12.74% ADR with Glimipride / Gliclazide followed by 11.21% with Metformin in users. Among the different ADRs reported from different system due to oral antidiabetic medications, most of the ADRs were of gastrointestinal origin.

Gastrointestinal System Adverse Drug Reactions: 43.75% of the total ADRs have been related to the gastrointestinal system. Dyspepsia was the most common gastrointestinal ADR seen in 3/16(18.75%) patients. Gastric irritation was seen in 2/16(12.5%) patients. Diarrhoea was seen in 1/16(6.25%) patients. Vomiting was observed in 1/16(6.25%) patients.

In our study, Dyspepsia has been observed as the most common adverse effect followed by gastric irritation, diarrhoea, and vomiting among the gastrointestinal system-related adverse effects. Dyspepsia has also been shown as the most common (116 out of 182 patients receiving oral antidiabetic medication) adverse effect by studies. Also, the incidence of dyspepsia shown in their study was 59.14% (84 out of 142) which is similar to our study finding of 60% (3 out of 5) for patients receiving metformin therapy alone in both. Studies have shown 30% incidence of dyspepsia in subjects receiving metformin medication. Saravanan *et al.,* [17] shows 25% (1 out of 4) incidence of gastric irritation as ADR in their study patients receiving combination therapy metformin plus glimipride which is nearly similar to our finding of 33.33% (2 out of 6) in the patients receiving same combination therapy. Diarrhoea was seen as an adverse effect in patients receiving metformin alone with ADR incidence of20% (1 out of 5), which is in lieu with findings of a study done by researchers showing 34.50% (49 out of 142) incidence of ADR with similar medication. Also 20% (1 out of 5) incidence of vomiting as ADR was seen in our study, which is in similar finding with a study of Saravanan *et al.,* [17] [102] showing 20% (2 out of 10)incidence of vomiting as an ADR with metformin alone as a medication in both.

Metabolic Disorder Adverse Drug Reactions: The overall contribution of metabolic de-rangements to the total ADRs came out to be 3/16 (18.75%). These were the second most common adverse drug reaction found in our study. The metabolic derangement which we came across was hypoglycaemia. It was observed that incidence of hypoglycaemia is equal to incidence of dyspepsia 3/16 (18.75%) although cases of hypoglycaemia were due to sulphonylurea (Glimipride/Gliclazide) and dyspepsia occurred in patients on metformin medication. Singh *et al.,* [16] have found hypo-glycaemia as ADR in 34.6% (9 out of 26) in their study patients and shows it as a most common adverse effect, which in our study came out to be the second most common adverse effect. Studies observed 92.5% (74 out of 80) incidence of this ADR in patients receiving glimipridealone, which is in lieu with our finding of 100% (2 out of 2) with the same medication.

Skin and Appendages Adverse Drug Reactions: In our study, adverse drug reactions related to skin and appendages contributed 2/16 (12.5%) of the total ADRs. The type of adverse drug reaction related to skin and appendages found in our study was an allergic reaction. This was found as 6.25% (1 out of 16) each with combination therapy metformin plus glimipride / gliclazide and metformin plus dipeptidyl transferase IV inhibitor. In study by Singh *et. al.,* [16] 15.3% (4 out of 26) ADRs were related to skin and appendages, which is in lieu with findings of the same in our study.

Musculoskeletal System Adverse Drug Reactions: In our study, musculoskeletal system-related adverse drug reactions contributed 2/16 (12.5%) of the total ADRs. A musculoskeletal disorder that we came across in our study was myalgia. This was found as 6.25% (1 out of 16) each with combination therapy metformin plus glimipride / gliclazide and metformin plus glimipride / gliclazide plus glitazone. In a study by Singh *et al.,* [16] 15.3% (4 out of 26) ADRs were related to musculoskeletal system, which is in agreement with findings in our study.

Central Nervous System Adverse Drug Reactions: The ADRs related to central nervous system adverse drug reaction contributed to 6.25% (1 out of 16) of total ADRs. The central nervous system-related adverse drug reaction we came across was dizziness which was seen in one patient receiving combination therapy metformin plus glimipride / gliclazide. 12.5% (2 out of 16) with glimipride and 40% (4 out of 10) with metformin incidence was found by Saravanan *et al.,* [17] in their study.

Respiratory System Adverse Drug Reactions: The ADRs related to respiratory system adverse drug reaction contributed to 6.25% (1 out of 16) of total ADRs. The respiratory system-related adverse drug reaction we came across was nasopharyngitis seen in one patient on combination therapy metformin plus dipeptidyltransferase IV inhibitor. Singh *et al.,* [16] has also shown near similar findings in their study; they found 3.8% (1 out of 26) incidence of respiratory-related ADR.

Adverse Effects with Different Drug Use: As discussed above, the % frequency of ADR has been described with oral antidiabetic medications (mono-therapy as well as combination therapy) prescribed. In our study, as monotherapy, metformin has been observed to be responsible for the occurrence of maximum ADRs 31.25% (5 out of 16) developed. This finding is in agreement with the findings of study done which showed that out of 48 adverse events reported, metformin was responsible for 87.5% of them which was the maximum. Similarly, the maximum percentage of total ADR was contributed by metformin 51.64% (142 out of 275) as shown in previous studies. Glimipride / gliclazide contributed 12.5% (2 out of 16) of total ADRs developed. It was found that among the mono as well as combination therapy, metformin plus glimepiride/gliclazide was observed to be responsible for occurrence of maximum ADRs 37.5% (6 out of 16) which is very near to the frequency of ADR occurrence with metformin alone in our study. Another combination therapy used in our study was metformin plus glimipride/gliclazide plus glitazone that contributed to 6.25% (1 out of 16) of total ADRs developed. Lastly, the combination therapy used in our study, metformin plus dipeptidyltransferase IV inhibitor, contributed to 12.5% (2 out of 16) of total ADRs developed.

Causality of the Adverse Drug Reactions: In our study, causality assessments of ADRs were done according to Naranjo scale, which categorises ADRs as "definite", "probable", "possible," and "doubtful". Of the 16 ADRs, five (31.25%) were categorized as probable, ten (62.5%) as possible and one (6.25%) as doubtful. Our finding of 31.25% (5 out of 16) of ADR having probable and 62.5% (10 out of 16) as possible causality is in agreement with the findings of study done by Singh et al16who observed 30.8% as probable and 69.2% as possible in their observation. Our finding shows that the maximum number of ADRs have a possible causal relationship with oral antidiabetic medications.

CONCLUSION: In our study regarding ADRs' assessment due to oral antidiabetic medications, we have come across the following conclusions: Out of these 206 patients studied, 120 patients were diagnosed with type II diabetes (alone/along with hypertension). Out of total 120 patients, male constituted more as compared to women. Age-wise distribution showed maximum number of patients belong to age group between 41-50 yr, which appeared to be the most vulnerable group. Duration of diabetes was ≤5 yr seen in maximum patients. Drug Prescription Pattern of oral antidiabetics showed that metformin was the most commonly prescribed drug followed by combination therapy of metformin plus glimipride / gliclazide. Out of 120 patients, 16 patients developed ADRs. The age group > 60 yrs being more vulnerable showed higher incidence and outnumbered the patients in another group who developed ADRs. As compared to females, there were more males with ADRs because males constituted more of our sample population. Out of 16 ADRs recorded, percent ADR frequency was seen maximum in patients prescribed Glimipride / Gliclazide alone that is 13.33% (2 out of 15). That shows more chances of ADR occurrence in these patients. A maximum number of the patients developing ADRs came up with adverse effects related to a gastrointestinal system like dyspepsia, diarrhoea, vomiting, gastric irritation.GIT was closely followed by symptoms related to metabolic disorders, hypoglycaemia, which is the common adverse effect seen with sulphonylurea therapy. Skin and Appendages related adverse drug reaction (allergic reaction) and musculoskeletal system related adverse drug

reaction (myalgia) presented with equal frequency. Central Nervous System related adverse drug reaction (dizziness) and respiratory system-related adverse drug reaction (nasopharyngitis) presented with equal frequency. A maximum number of ADRs were seen with combination therapy of metformin plus glimipride / gliclazide followed by metformin monotherapy. On the assessment of causality through Naranjo's algorithm, maximum of the adverse drug reactions have been categorized under "possible," which is being followed by category of "probable" (31.25%; 62.5%) suggesting that due to lack of dechallenging and rechallenging in the process of causality assessment, none of the ADRs can be grouped under "definite". We can conclude that only vigilance about known and unknown ADRs, assessment of their causality, and prompt management can mitigate toxicity. By monitoring laboratory and clinical parameters and instituting appropriate measures, the frequency and severity of known ADRs can be reduced. This may help improve the compliance and, ultimately, quality of patient care. Thus, finally, for treatment adherence and to improve outcome in disease, close monitoring and timely management of adverse drug reactions are essential.

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ETHICAL APPROVAL: The study was approved by the Institutional Ethics Committee.

CONFLICTS OF INTEREST: None declared.

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