Research Article

# Evaluation of Suspected Adverse Drug Reactions of Oral Anti-diabetic Drugs in a Tertiary Care Hospital for Type II Diabetes Mellitus

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## ABSTRACT

**Background and Objective:** The objective of the study was to evaluate and analyse ADRs in type II diabetic patients and to determine the causality, severity and preventability of reactions. **Methods:** 460 diabetic patients on oral anti-diabetic drugs were evaluated prospectively over a period of six months. All patients were followed up for ADRs which were evaluated for incidence, frequency, severity and causality. Causality was graded according to WHO-UMC scale and Naranjo scale. Severity according to Modified Hartwig and Siegel scale and preventibility based on Modified Schumock and Thornton Scale. **Results and Discussion:** A total of 58 ADRs were reported from 460 patients during the study period with female predominance over male. All the ADRs that were reported were of type A category. The class of drug responsible for causing more ADRs was found to be biguanides. The most commonly affected organ system was GI System The suspected ADRs were assessed for their causality, it was revealed that 52 were probable and 6 were possible and as per Naranjo scale 53 were probable and 5 possible. The ADRs were assessed for severity using Modified Hartwig and Siegel scale and it was observed that 28 were mild and 30 moderate. Preventibility of reported ADR cases was assessed using the Modified Schumock and Thornton Scale. Using this scale all 58 ADRs were probably preventable. **Conclusion:** These study results provide insight to the healthcare providers on the importance of monitoring and reporting ADR associated with the drugs.

**Key words:** Adverse Drug Reaction, WHO-UMC Scale, Naranjo Scale, Modified Hartwig and Siegel scale, Modified Schumock, Thornton Scale.

## INTRODUCTION

Diabetes is a metabolic diseases characterized by hyperglycemia due to defects in insulin secretion, insulin action or both. The chronic characteristic of diabetes is associated with long-term damage, dysfunction and failure of various organs like eyes, kidneys, nerves, heart and blood vessels.[1]

As per International Diabetes Federation (IDF) calculation, the number of people with diabetes in the world in 2013 was 382 million, which can increase up to around 592 million in the coming years. India has been home to a large population of people from diabetes. According to IDF, 65.1 million of adults in India suffered from diabetes in the year 2013. It has been predicted that the occurrence of diabetes among adult population in India will be 6% by the year 2025.

The management principles of diabetes focus on disease prevention, screening high risk individuals and aggressive treatment of individuals in the pre-diabetic state. Pharmacological treatment remains the main option for most of these patients.[2] The conventional options for type II diabetes mellitus include drugs that have been relatively long on the market such as Biguanides, Sulfonylureas (SU), Alpha-glucosidase inhibitors, Meglitinides, Thiazolidinedione (TZD), Dipeptidyl Peptidase 4 Inhibitors and Sodium Glucose Co-transport 2 Inhibitors. Drugs are the commonest medical interventions used to relieve sufferings but drugs themselves can prove fatal and can result in adverse drug reactions (ADR) which can be mild to serious. Inspite of their efficacy by achieving glycaemic control, there are some safety

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issues with antidiabetic drugs such as gastro-intestinal problems, metabolic disorders, central nervous system (CNS) disorders, muscoskeletal disorders, genito-urinary disorders, peripheral oedema, nasopharyngitis, weight gain etc.[3-4]

World Health Organisation (WHO) defines adverse drug reactions as any response to a drug which is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiologic function. Thus, this definition excludes over dose (either accidental or intentional), drug abuse, failure of treatment and errors of drug administration.[5-7]

Diabetic patients requires prolonged treatment and continuous follow up but due to lack of knowledge many of them continue to take the same drugs continuously without monitoring proper blood sugar level.[8-10] So, they continue to take the same drug and become un aware of adverse drug reactions and detection of ADR becomes impossible. Therefore, the medications must be individualized for each patient by balancing the potential for lowering HbA1c and anticipated long-term benefit with specific safety issues, as well as by considering regimens including side effects, ease of use, long-term adherence, expense etc.[11,12]

The detection of Adverse Drug Reactions (ADRs) has become significant because of introduction of large number of drugs in the last two decades. Adverse drug reactions may occur daily in hospitals a adversely affecting patients life, often causing considerable morbidity and mortality. Attention should be given in identifying the patient populations at danger the drugs most commonly responsible and the causes of ADRs. Increased supply of drugs in the market and an upward trend in polypharmacy are contributing factors to the prevalence of ADRs worldwide. Adverse drug reactions can result in loose of patients confidence leading to negative emotions toward their physicians treatment and can engage in self-treatment options, which may consequently precipitate additional ADRs.[12,13]

WHO has seriously considered this matter by establishing an international adverse drug reactions monitoring centre at Uppsala, Sweden, which is collaborating with national monitoring centers in around 70 countries. The first ADR monitoring programme started with 12 regional centers and India joined the WHO monitoring program Uppsala, Sweden in 1997 and three centers were started in medical colleges at New Delhi, Mumbai and Aligarh.[14-17] By July 2010 a nationwide revised ADR monitoring programme started named as pharmacovigilance programme of India under the Health Ministry, Government of India. In India, much attention is not given so far and very few studies have been done on this. We have very few ADR monitoring centers and lot of efforts is required in order to collect ADR data for generating safety surveillance of billions of pharmacologicaly active substances.[18-20]

## MATERIALS AND METHODS

### Study Site

The study was conducted in out-patients of Endocrinology Department of Iqraa International Hospital and Research Centre, Calicut.

### Study Design

The prospective observational study was carried among 460 patients with diabetes attending out-patient endocrinology department to evaluate the incidence, frequency, severity and causality.

### Study Population

Patients taking treatment for type II diabetes mellitus.

### Study Duration

The study was carried out for a period of 6 months (January 2017-June 2017).

### Study Criteria

### Inclusion Criteria

Out-Patients of endocrinology department taking oral hypoglycemic agents for type II diabetes patients of both sex.

### Exclusion Criteria

### In-patients

Adverse drug reaction due to over dosing, diabetic nephropathic patients, intensive care patients and gestational diabetic patients are excluded.

### Study Procedure

Data were collected from patients undergoing treatment of diabetes mellitus in endocrinology department in Iqraa International Hospital and Research Centre were selected and was interviewed and recorded. All relevant data including various demographics, drugs received by patient, their dosage and duration of disease were collected.

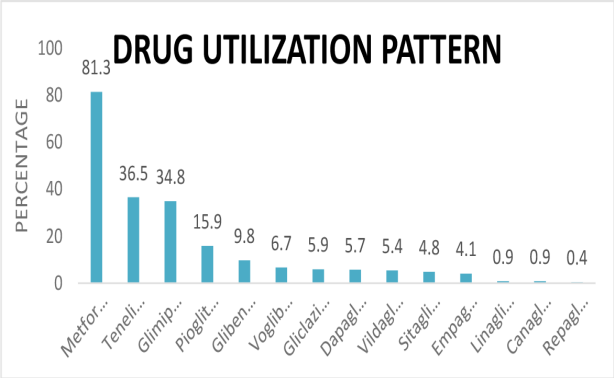


**Figure 1:** Drug utilization pattern of antidiabetic drugs.

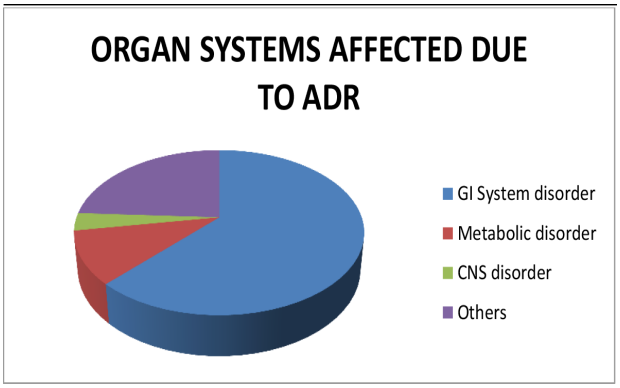


**Figure 4:** Organ system affected The most affected system was GI system

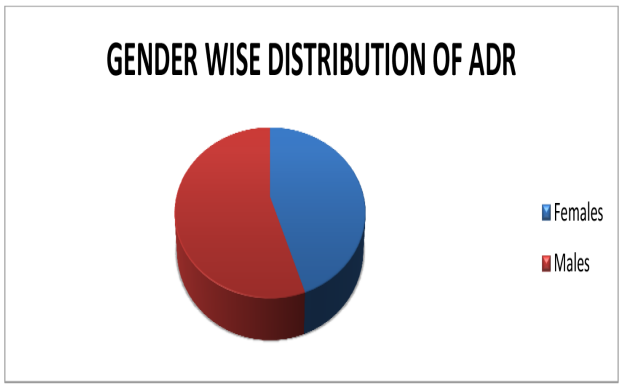


**Figure 2:** Gender wise distribution of ADR , showing female predominance

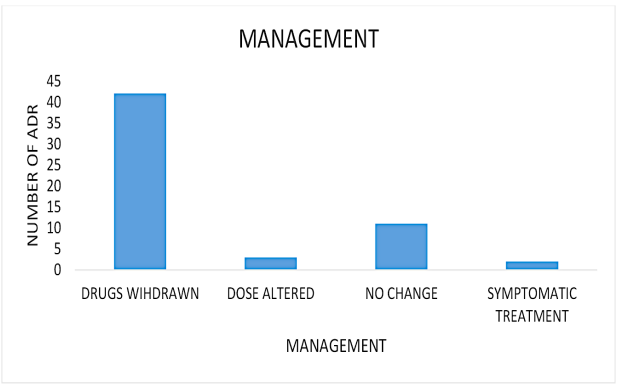


**Figure 5:** Management of ADR occured In managing ADR drugs were withdrawn for 42 cases, no change for 11 and dose was altered for 3 and symptomatic treatment given for 2 patients.

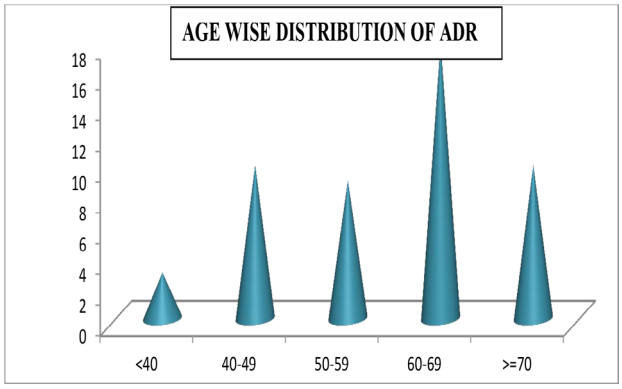


**Figure 3:** AGE WISE DISTRIBUTION OF ADR ADR was more predominant in geriatric population.

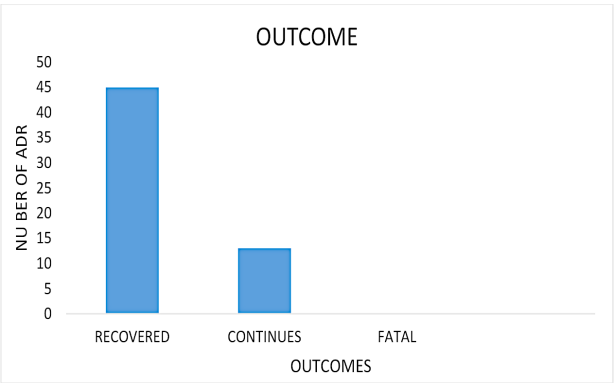


**Figure 6:** Outcome of reported ADR Out of 58 ADR's 45 recovered and 13 reactions still continued, ther were no fatal reactions.

## RESULTS

### Patient Demographics

### Gender Distribution

Table 1 shows that among 460 patients, 279 (60.7%) were females and 181 (39.3%) were male.

### Age Distribution

Age wise distribution geriatric patients were more accounted.

Table 2 shows that 30.2% of the patients were in the age group of 50-59 and less percentage were seen in age group of less than 40.

### Drug utilization pattern of anti-diabetic drugs

From this study around 81.3% of the patients were taking biguanides, followed by teneligliptine (36.5%)

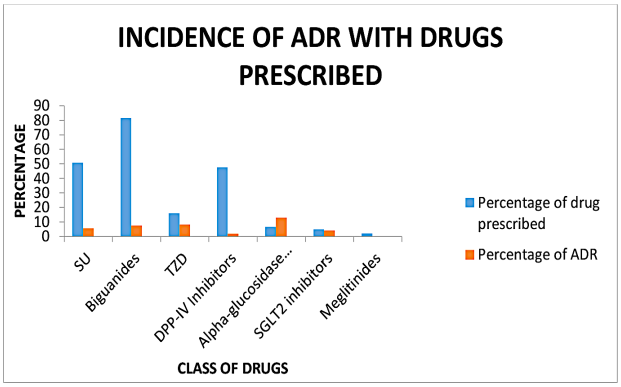


**Figure 7:** Incidence of ADR with drugs, The mostly prescribed drug was biguanide class of drugs but ADR with that class of drug is less whereas less prescribed drug class alpha-glucosidase inhibitors shows more ADR than prescibed percentage. So the more prescribed drug shows comparitively less incidence of ADR and it is safe

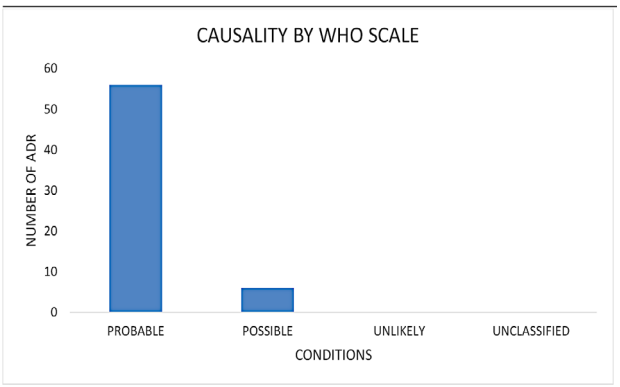


**Figure 8:** Causality assessment-WHO Scale, Causality assessment by WHO scale shows that 52 ADRs were probable and 6 were possible

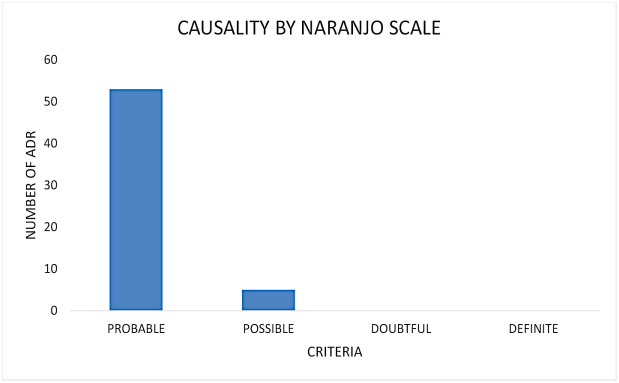


**Figure 9:** Naranjo causality assessment, 53 were probable reactions and 5 were possible.

and glimipride (34.8%) rest of the drugs having lesser percentage as shown in Figure 1.

## ADR occurrence

Among 460 patients 50 (10.9%) patients experienced ADR and out of that 8 patients had more than 1 ADR.

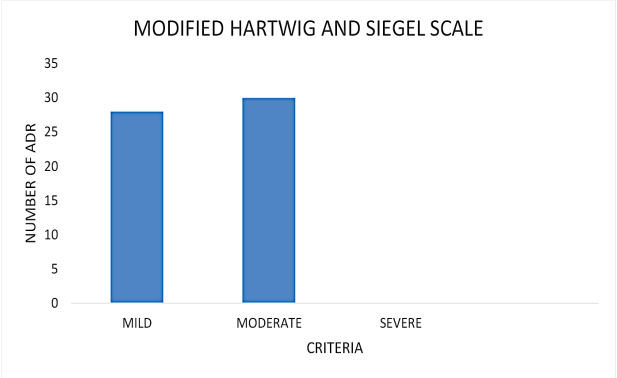


**Figure 10:** Severity Assessment, 28 reactions were mild and 30 were moderate

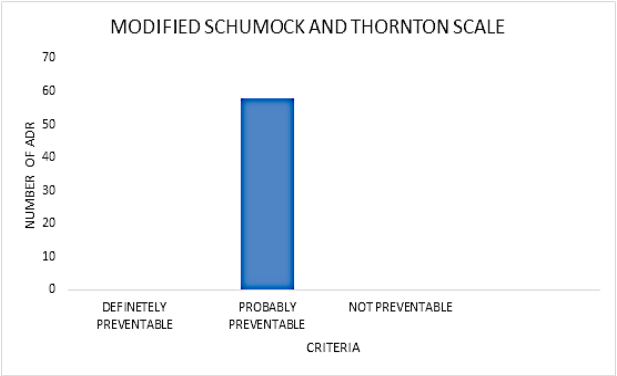


**Figure 11:** Preventability assessment scale, All the ADR were probably preventable

**Table 1: ADRs are more pronounced in females compared to male**

| GENDER | FREQUENCY | PERCENTAGE |
|---|---|---|
| Female | 279 | 60.7 |
| Male | 181 | 39.3 |
| Total | 460 | 100 |

**More numbers of ADRs are mainly seen in geriatric populations**

| AGE GROUP | FREQUENCY | PERCENTAGE |
|---|---|---|
| <40 | 38 | 8.3 |
| 40-49 | 107 | 23.3 |
| 50-59 | 139 | 30.2 |
| 60-69 | 125 | 27.2 |
| >=70 | 51 | 11.1 |
| Total | 460 | 100 |

The most commonly identified ADRs were with Biguanides followed by Sulfonylureas, TZD, DPP-4 inhibitors, Alpha-glucosidase inhibitors and SGLT2.

**Table 3: Indicates the list of ADR associated with drugs, in which metformin has more number of ADRs**

| CLASS OF DRUG | NAME OF DRUG | NO: OF ADR | ADR |
|---|---|---|---|
| Sulfonylureas | Glimepride | 7 | Hypoglycaemia, Weight gain, Dizziness, Gastric irritation. |
| | Glibenclamide | 3 | Hypoglycaemia, Weight gain |
| | Gliclazide | 3 | Vomiting, Weight gain, Gastric irritation |
| DPP-IV inhibitors | Teneligliptine | 4 | Hypoglycemia, Weight gain, Oedema |
| SGLT2 inhibitors | Canagliflozin | 1 | Constipation |
| | Dapagliflozin | 1 | Constipation |
| TZD | Pioglitazone | 6 | Weight gain, Oedema |
| Alpha-glucosidase inhibitors | Voglibose | 4 | Bloating, Dyspepsia, Gastric irritation, Diarrhoea |
| Biguanides | Metformin | 28 | Gastric irritation, Dizziness, Decreased appetite, Tiredness, Metformin Intolerance, Vomiting, Dyspepsia |

**Table 4: Types of ADR**
**Only type A reactions were noted**

| TYPES OF ADR | NUMBER OF ADR |
|---|---|
| Type A | 58 |
| Type B | 0 |

**Table 5: Organ system affected**
**GI system was more affected**

| System Affected | ADR | NUMBER OF ADRs | TOTAL |
|---|---|---|---|
| GI system disorders | Dyspepsia | 1 | 36 |
| | Diarrhoea | 1 | |
| | Constipation | 2 | |
| | Metformin Intolerance and gastric irritation | 24 | |
| | | 1 | |
| | Bloating | 1 | |
| | Vomiting | 6 | |
| | Decreased appetite | | |
| Metabolic disorders | Hypoglycaemia | 6 | 6 |
| CNS disorders | Dizziness | 2 | 2 |
| Others | Oedema | 5 | 14 |
| | Tiredness | 1 | |
| | Weight gain | 8 | |

**Table 6: Management carried out**
**Most of the drugs were withdrawn**

| MANAGEMENT | NO: OF PATIENTS |
|---|---|
| Drug Withdrawn | 42 |
| Dose altered | 3 |
| No change | 11 |
| Symptomatic treatment | 2 |

**Table 8: Indicates the incident rate of ADR with drugs prescribed. The more commonly prescribed drug has less percent of ADR, that is more safe whereas less prescribed drugs have more ADR**

| CLASS OF DRUGS | NUMBER OF DRUGS PRESCRIBED | PERCENTAGE OF DRUGS PRESCRIBED | ADR REPORTED | PERCENTAGE OF DRUG PRESCRIBED WITH ADR (%) |
|---|---|---|---|---|
| SU | 234 | 50.9 | 13 | 5.6 |
| Biguanides | 375 | 81.5 | 28 | 7.5 |
| TZD | 73 | 15.9 | 6 | 8.2 |
| DPP-IV inhibitors | 219 | 47.6 | 4 | 1.8 |
| Alpha-glucosidase inhibitors | 31 | 6.7 | 4 | 12.9 |
| SGLT2 inhibitors | 49 | 5 | 2 | 4.1 |
| Meglitinides | 2 | 0.4 | 0 | 0 |

**Table 9: WHO CAUSALITY ASSESSMENT SCALE, 52 reactions were probable and 6 were possible**

| CONDITIONS | NUMBER OF ADR |
|---|---|
| Certain | 0 |
| Probable | 52 |
| Possible | 6 |
| Unlikely | 0 |
| Unclassified | 0 |

**Table 7: OUTCOME OF ADR**
**45 recovered while 13 reactions still continued**

| OUTCOME | NO: OF PATIENTS |
|---|---|
| Recovered | 45 |
| Continues | 13 |
| Fatal | 0 |

**Table 10: Naranjo causality assessment scale**
**53 ADRs were probable and 5 were possible**

| CONDITIONS | NUMBER OF ADR |
|---|---|
| Definite | 0 |
| Probable | 53 |
| Possible | 5 |
| Doubtful | 0 |

**Table 11: Severity assessment by modified Hartwig and Siegel scale**
**28 ADR were mild and 30 moderate**

| CONDITIONS | NUMBER OF ADR |
|---|---|
| Mild | 28 |
| Moderate | 30 |
| Severe | 0 |

**Table 12: Preventability assessment by modified Schumock and Thornton scale**

| CONDITIONS | NUMBER OF ADR |
|---|---|
| Definitely Preventable | 0 |
| Probably Preventable | 58 |
| Not Preventable | 0 |

### Gender wise distribution of ADR

The study revealed that the female population 28(6.08%) predominated over male patients 22 (4.8%) in ADR occurrence represented in Figure 2 and Table 1.

### Age wise distribution of ADR

The age wise distribution revealed that the incident rate of ADR were more in age group of 60-69 (18) given in Table 2, Figure 3.

### Types of ADR (*n*=58)

Only type A ADR (58) were reported and there was no type B reactions as in Table 4.

### Organ system affected due to ADR Management carried out (*n*=58)

Methods carried out in managing the ADR are, drugs were directly withdrawn in 42 cases, in 11 cases no changes were done, dose was altered in 3 cases and symptomatic treatment was provided in 2 cases shown in Figure 5 and Table 6.

### Outcome of ADR (*n*=58)

Table 7 and Figure 6 indicate that 45 of the ADRs were recovered and 13 reactions still continued and there were no fatal evidence.

### Incidence of ADR with drugs prescribed

When we are comparing the number of drugs prescribed with the ADRs observed, it is found that the incidence rate of ADR with the more commonly prescribed drugs were comparatively less indicated in Figure 7 and Table 8. Here the more number of ADR was seen with Bigunides but when comparing it with the total number of drugs prescribed the incidence rate of ADR with respect to biguanide is less.

### Who Causality Assessment Scale (*n*=58)

Causality assessment by using WHO scale categorized 52 ADRs as probable and 6 were possible (Table 9 and Figure 8).

### Naranjo Causality Assessment Scale (*n*=58)

Causality assessment by using Naranjo scale indicated that majority of the ADRs (53) were probable and (5) were possible which is represented in Figure 8, Table 9.

### Severity assessment by modified Hartwig and Siegal scale (*n*=58).

The severity assessment using modified Hartwig and Siegal scale indicated that the majority of the ADRs were mild followed by moderate respectively given in Table 11 and Figure 10.

### Preventability Assessment Modified Schumock and Thornton Scale (*n*=58)

From Table 12 and Figure11, preventability assessment using modified Schumock and Thornton revealed that all the ADR were probably preventable.

## DISCUSSION

In the study a total of 460 diabetic patients were encountered and 58 ADRs were detected from 50 patients (10.9%) with a predominance of female gender (6.8%) over males (4.8%). Majority of patients in the study was also females. Patients in the age group of 60-69 years experienced maximum ADRs (18), which is in accordance

with the study of Bhattacharjee *et al.*[9] which shows that the incidence of ADR is more in geriatric population. Majority of the ADR cases were seen in patients taking medication for a period of less than 5 years which is similar to the study carried out by Javedh Shareef *et al.*[21]

Only type A ADR were reported in all the cases. The most commonly prescribed anti-diabetic medication was metformin, which was also responsible for causing more number of ADRs, but when analyzing the safety of drug, metformin was prescribed in 375 patients but only 28 ADRs were reported, which is similar to study conducted by Tirthankar Debet *et al.*[19]

Organ system most commonly affected was gastro intestinal system (36) which was similar to the study conducted by Singh H *et al.*[18] As a part of management in 42 cases the drug was withdrawn, no changes were done in 11 cases, dose altered in 3 cases and symptomatic treatment was provided in 2 cases. Adverse drug reaction encountered were treated and the final outcome was measured. About 45 ADRs were recovered and 13 were continuing.

In order to strengthen and further emphasize the validity of the study, causality assessment was done using Naranjo scale and WHO-UMC scale. The assessment showed that out of 58 ADRs, (52) were probable and (6) were possible as per WHO scale and Naranjo scale indicated that majority of the ADRs (53) were probable and (5) were possible. These findings are similar to the study carried out by Javedh Shareef *et al.*[21] which stated that most of the ADRs belong to category probable. On the evaluation of the severity of ADRs by the Hartwig and Siegel severity assessment scale, it was evident that most of the ADRs reported in the study were moderate (30) in nature followed by 28 were mild No lethal outcomes were observed or produced during the study period. Assessment of the preventability of the ADRs using modified Schumock and Thornton scale revealed that 58 ADRs were probably preventable.

When analyzing the safety of drugs, in the study more number of ADRs (28) were reported with biguanides similarly most commonly prescribed drug (375) was also metformin. Therefore, the incidence rate of ADR with the drug is comparatively less ie only 7.5%, whereas in case of Thiazolidinedions 6 ADRs were reported from 73 prescriptions and the incidence rate of ADR with Thiazolidinedions was 8.2%. In case of Alpha-glucosidase inhibitors 4 ADRs were reported from 31 prescriptions and the incidence rate of ADR with Alpha-glucosidase inhibitors is 12.9%. Therefore, metformin is considered as the safest drug when compared to the newer classes of drugs and is prescribed more commonly.

## CONCLUSION

ADRs are drug related problems which is considered as important drawback for drug safety. The spontaneous reporting used in study allowed the detection and characterization of ADRs. The present study has provided information regarding the prevalence of ADRs and their distribution among different age groups, genders, organ systems affected and therapeutic classes of medicines. The data presented here will be useful in future for extensive ADR monitoring and will be useful in rational use of drugs.

Monitoring of adverse drug reactions is a continuing process. As newer and newer drugs are being introduced in the market, the need for pharmacovigilance is important than ever before. Monitoring of ADRs in patients taking oral anti-diabetic agents is very important since such medications have to be continued lifelong so it is very essential to monitor those drugs as it is well known to cause ADRs like GI disturbances, edema, hypoglycemia, weight gain etc. As the newer drugs are increasingly being prescribed in Indian scenario, hence the need of ADR monitoring is growing ever than before. It is also important to persuade health care professionals to understand their responsibilities in identifying, management, recording and reporting of ADRs for optimizing drug safety.

Avoidable ADR can be reduced by more skillful prescribing. Providing knowledge and awareness of ADRs reporting among health care professionals would introduce

the reporting among medical practitioners and increase the reporting rates of ADRs. Careful involvement in planning and monitoring of drug

therapy will lead to prevention of ADRs. This study suggests that ADR in hospital-based monitoring is a good method to detect known and unknown links between drug exposure and ADRs. A good relationship also needs to be framed between doctors and pharmacovigilance centers so that they consider ADR reporting as an integral part of their clinical activities. It is needed to make aware the treating doctors about the importance of observing for ADR, recording them continously and reporting them to the concerned authority. This practice will prove to be very valuable in making the drug therapy safer and rational. In future a comprehensive Programme is required in each level of health care system starting with treating doctors, nurses, paramedics and drug dispensing

pharmacist to ensure better and safe pharmacotherapy and improve compliance of patients.

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## CONFLICT OF INTEREST

No conflict of interest.

## ABBREVIATIONS

**ADR:** Adverse Drug Reaction; **ASHP:** American Society of Health-System Pharmacists; **ATP:** Adenosine Triphosphate; **BNF:** British National Formulary; **CNS:** Central Nervous System; **CSM:** Committee on Safety of Medicines; **CVD:** Cardiovascular Disease; **DM:** Diabetes mellitus; **DPP-IV:** Dipeptidyl Peptidase-IV; **FDA:** Food and Drug Administration; **GLP-1:** Glucagon-Like Peptide-1; **HIV:** Human Immuno Deficiency Virus; **IDF:** International Diabetes Federation; **IDDM:** Insulin-Dependent Diabetes Mellitus; **PCOS:** Poly Cystic Ovarian Syndrome; **PPAR – γ:** Peroxisome proliferator activated receptor-gamma; **SGLT-2:** Sodium Glucose Co-Transport 2; **SU:** Sulfonylureas; **SUR:** Sulphonyl Urea Receptor; **TZD:** Thiazolidinedione; **UMC:** Uppsala monitoring Centre; **WHO:** World Health Organization.

## SUMMARY

The study concludes that the need of ADR monitoring is growing ever than before so, it is necessary to motivate health care professionals to understand their responsibilities in detection, management, documentation and reporting of ADRs for optimizing drug safety.

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