

# To Assess the Causality, Severity and Preventability of Adverse Drug Reactions of Metformin in Treatment of Diabetes

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**Abstract:** Metformin is biguanide anti-hyperglycemic drug which is commonly prescribed hence it become essential to evaluate hospital based adverse drug reactions to identify risk associated with metformin. The objective of the study was to evaluate and analyzed adverse drug reactions in type 2 patients consuming metformin and determine causality, severity and preventability of adverse drug reactions. **Background and objective:** The objective of the study was to evaluate and analyze ADRs in type II diabetes patients and to determine the Causality, severity, and preventability of reactions. **Methods:** The study was done on 30 patients prescribed with metformin in local diabetic care hospital over a period of 30 days. All patients were followed up for adverse drug reactions which were evaluated for causality, severity and Preventability. Causality was evaluated according to Naranjo scale, severity according to Hartwig and Siegel scale, and preventability based on modified Schumock and Thornton scale. **Results and discussion:** A total 19 ADRs were reported from 30 patients during the study period. All ADRs that were reported were type A category. The most commonly affected organ was gastrointestinal system. 6 ADRs were probable and 1 was possible as per Naranjo scale. 16 ADRs were reported mild and 3 ADRs were moderate according to Hartwig and Siegel severity assessment scale. The reported adverse drug reactions were probably preventable. **Conclusion:** These study results provide insight on the healthcare providers on the importance of monitoring and reporting ADRs associated with drugs.

**Keywords:** Metformin, Adverse Drug Reaction, Naranjo scale, Hartwig and Siegel scale

## 1. Introduction

Diabetes mellitus is a complex chronic illness associated with a state of high glucose level or hyperglycemia. Type 2 diabetes is non-insulin dependent diabetes mellitus (NIDDM). It accounts for about 90% of the diagnosed cases of diabetes and affects 18% of the population over 65 years of age. Metformin is most commonly used drug in treatment of diabetes mellitus type II. It includes in class biguanides. The biguanides are derivatives of the compound biguanide that exert a blood glucose lowering effect in type 2 diabetes mellitus. The main biguanides are Metformin, phenformin and buformin. Phenformin and buformin were withdrawn from clinical use due to high incidence of lactic acidosis. Metformin has much lower risk of lactic acidosis.

Type 2 is more associated with an adulthood and elderly people, which are mainly due to insulin resistance are unknown, but they are associated with the disease state, environmental impact and food habit. Diabetic patients are more susceptible to various types of infection such as skin diseases and Carbuncles. Other type of diabetes is gestational diabetes which is mainly associated with Pregnancy. Genetic defects of beta-cell function or insulin action is also a type of diabetes Mellitus commonly called maturity onset diabetes. Number of people older than 64 years with diabetes will be greater in developing countries.

The Naranjo's causality algorithm is widely used to determine whether an ADR was actually due to the drug identified by the clinical event monitor, rather than the result of other factors. Naranjo scale consists of a questionnaire of 10 questions and answers of these questions are YES or NO type. According to this the scores are given.

Severity assessment is very important in pharmacovigilance studies of adverse drug reactions. It can be assessed by the Hartwig and Siegel severity assessment method. The

assessment is based on various levels that described in this method. Preventability can assess by Schumock and Thornton assessment method both these methods are frequently and most used for ground level studies and studies that are conducted using spontaneous methods of reporting.

ADRs reporting programmes can provide valuable information about the issues associated with medication. In addition, the ability to detect ADRs and generate new signals would enhance pharmacovigilance system. Good pharmacovigilance helps in the minimization or prevention of ADRs through early detection and effective communication, which ultimately help each patient to receive optimum therapy. It can enhance the patients trust on medication and treatments. The detection, management, prevention, and reporting of ADR is most important in improving patient care and to reduce cost. This present study is aimed to strengthen the ADR database through analysis and reporting of ADRs. Hence aim of this study was to examine the ADRs in a tertiary care hospital and access the type causality preventability and severity of the ADRs. the present study intended to monitor ADRs in tertiary care hospital; where the clinical pharmacy service established.

## 2. Materials and Methods

### 2.1 Study Design

The survey was conducted on outpatients of local diabetic care hospital having diabetes mellitus type II. The prospective observational study was carried out among 30 diabetic patients to evaluate causality severity and frequency of ADRs associated with drug Metformin.

**2.2 Methodology**

The data is collected from hospital outpatients by spontaneous reporting method of pharmacovigilance. The data collected includes demographic details of patients such as age and gender. Information about ADRs associated with Metformin is collected by asking patients questions. Causality assessment was determined using Naranjo scale. severity of ADRs were determined and ADRs are classified as mild, moderate, severe and lethal Furthermore, preventability of ADRs determined using Schumock and Thornton criteria.

**Study duration**

The study was carried out for period of 30 days (May 2022- June 2022)

**Study criteria**

**Inclusion criteria**

- Out patients diagnosed with diabetes mellitus type II and prescribed with drug Metformin.
- Patients with both sexes has examined.

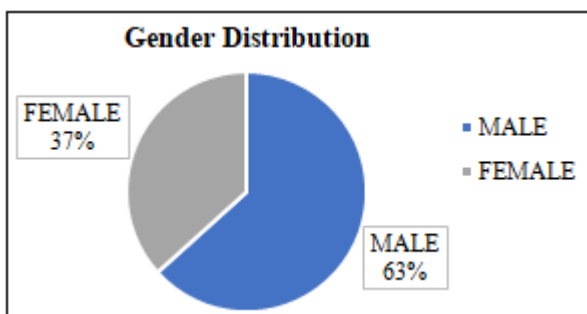
**Exclusion criteria**

- Intensive care patients
- Hospitalized patients
- Patients having treatment with insulin and other drugs excluding Metformin.
- Patients who were unwilling to participate and did not give consent in the study.

**Demographics of patients**

**Gender distribution**

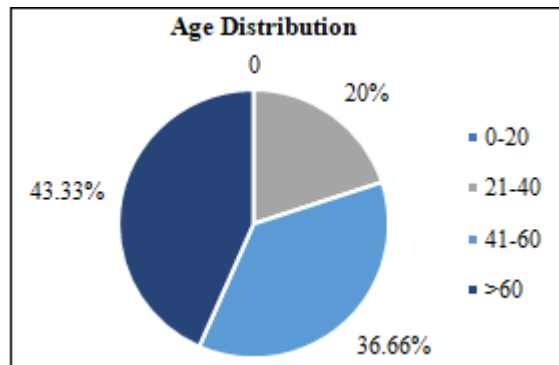
The data of total 30 patients of Saidutta Hospital, Wai, Maharashtra Were collected out of which 19 were male patients and 11 were female patient.



**Figure 1**

**Age distribution of ADRs**

From the collected data it is observe that among 30 patients 13 patients were more than 60 age and patient less than 20 age were not accounted.



**Figure 2**

**Adverse drug reactions reported by patients**

The data of 30 patients were collected from diabetic care hospital. To obtained data of adverse drug reactions of these patients were asked about any side effects they observed after using the drug metformin. Among these 30 patients only 19 ADRs were reported from 14 patients and rest of the 16 patients has not detected any ADRs.

According to study conducted on drug metformin the adverse drug reactions associated with this drug are pain in muscle, abdominal pain. low blood sugar, heart burn, full feeling, indigestion, passing of gas, loss of appetite, vomiting, metallic taste in mouth, flu like symptoms, headache and metformin associated lactic acidosis (MALA). Lactic acidosis is increased in concentration of lactic acid in blood which can cause due to overdose of metformin which is very rare side effect of metformin

These adverse effects can be overcome by reducing the dose of metformin or by replacing it with another drug.

**Table 1: Frequency of ADRs**

S. No.	Adverse Drug Reactions	Frequency
1	Weakness / muscle pain	3
2	Abdominal pain	1
3	Loss of appetite	4
4	Decrease level of vit B 12	2
5	Bloating /indigestion	5
6	Gastric irritation	4
7	Nausea / vomiting	0
8	Metallic taste in mouth	0
9	Hypoglycemia	1

**Causality assessment of metformin**

Causality assessment is the assessment of relationship between a drug treatment and the occurrence of an adverse event. It is an essential part of ADR report and important task conducted by national pharmaco vigilance Programme in each country. Causality is the key factor for identification of new signals measuring the strength of signals measuring the strength of evidence and in evaluating benefit risk profile of pharmaceutical medicinal products. There are various published methods for causality assessment in ADRs and all have advantages and limitations. The main purpose of developing standardized causality assessment system is to provide reliable and reproducible measures of the possible relationship in suspected cases of ADRs. It is often difficult

to decide if an adverse clinical event is an ADR or due to deterioration in the primary condition.

There are three common methods of causality assessment

- 1) WHO causality assessment
- 2) Global introspection or clinical judgement
- 3) Naranjo causality assessment

In which Naranjo causality assessment is most popular and commonly used in clinical research and pharmacovigilance.

There is a questionnaire of some questions that are answers as either yes or no or don't know different point values are assigned to each answer. The obtained results are classified ADRs into definite, probable, possible and doubtful. Values obtained from the algorithm are sometimes used in peer reviews to verify the validity of authors conclusions regarding adverse drug reactions. It is also called Naranjo Scale or Naranjo Score.

The survey was conducted on 30 patients having diabetes mellitus type II and continuing treatment with metformin

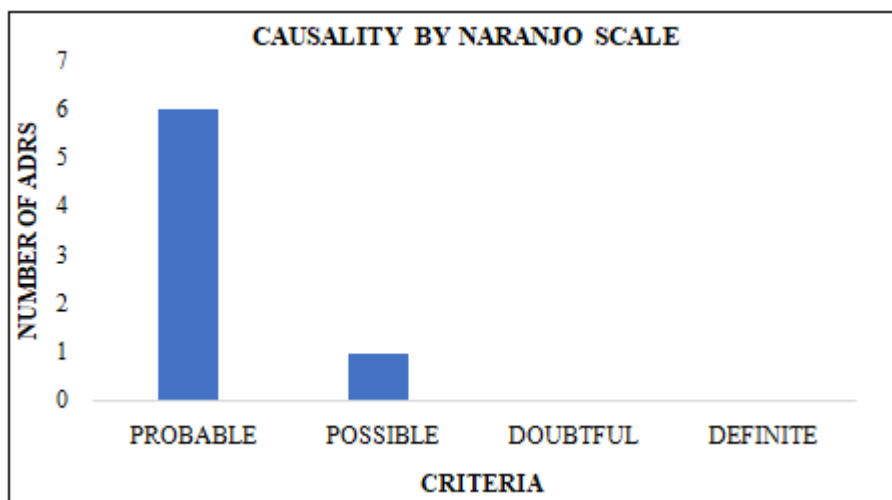


Figure 2

Table 2: Naranjo scale

S. no	Please answer the following questionnaire and given the pertinent score	Yes	No	Don't know
1	Are the previous conclusive reports on this reaction?	1		
2	Did the adverse drug event appear after the suspected drug was given?	2		
3	Did adverse reaction improve when drug was discontinued or a specific antagonist was administered?			0
4	Did adverse drug reaction reappeared when the drug was readministered?	2		
5	Are there alternative causes (other than drug) that could have on their own caused the reaction?	-1		
6	Did the reaction reappear when the placebo was given?			0
7	Was the blood detected in the blood (other than fluids) in concentrations known to be toxic?		0	
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1		
9	Did the patient have similar reaction to the same or similar drug in any previous exposure?		0	
10	Was the adverse event confirmed by any objective evidence?	1		

Table 3: Naranjo score

definite	if the overall score is 9 or greater
probable	for a score of 5-8
possible	for 1-4
doubtful	if the score is 0

The assessment showed that out of 19 ADRs, majority of ADRs are probable

### Severity assessment of metformin

The term severity is used to describe the intensity of medical event and is graded as minor, severe, and lethal. There are certain reactions that are life threatening such as liver failure, high blood pressure, disability that results in hospitalization are known as severe ADRs. Severe reactions relatively rarely happen. Those reactions in which a drug can causes death directly or indirectly are considered as lethal reactions. There are definite reporting time frames for different types of ADRs such as fatal or life threatening

unexpected ADRs are must be reported within 7 calendar days. Mild ADRs are those which require no change in treatment with suspected drug. Moderate ADRs is that requires treatment with suspected drugs be held, discontinue or otherwise change and antidote or other treatment was required without increase in length of stay.

Hartwig and Siegel severity assessment is used in measurement of severity. It classified ADRs into 7 levels of severity

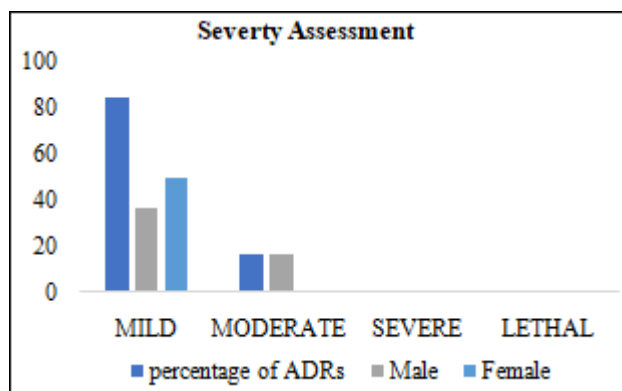
Table 4: Severity levels

levels	Category	Characterization
Level 1 & 2	Mild	Requires no change in treatment with suspected drug
Level 3 & 4	Moderate	Suspected drug be withheld changed or discontinue
Level 5, 6 & 7	Severe	ADRs requires intensive medical care or hospitalization.

A prospective, observational study of diabetes mellitus type 2 was carried out in 30 patients in local diabetic care Hospital. A total 30 patient were followed up. The severity was evaluated with the classification provided in Hartwig's severity assessment scale

**Table 5: Severity assessment**

Sr no	Type of severity	No of ADR	Sex distribution (%)	
			Male	Female
1	Mild	16 (84.21)	7 (36.84)	9 (49.99)
2	Moderate	3 (16.66)	3 (16.66)	0
3	Severe	0	0	0
4	Lethal	0	0	0



**Figure 3**

**Preventability assessment**

Preventability assessment helps in improving drug use Preventability assessment of ADRs of metformin was evaluate using Schumock and scale. Inschumock and Thornton criteria there are three sections definitely preventable, probably preventable, not preventable. Section A has five questions while section B has4 questions. All questions are categorized as yes or no type

**Table 6: Preventability assessment**

Conditions	Number of ADRs
Definitely preventable	0
Probably preventable	19
Not preventable	0

The data obtained from the survey shows that ADRs associated with drug metformin is probably preventable

**3. Results and Discussion**

In study of patients with diabetes mellitus type II it was found that most commonly prescribed drug is Metformin. Total 30 no. Of patients of diabetes mellitus were encountered. The patients were prescribed with drug Metformin. Among 30 patients 19 ADRs were detected from 14 patients. The remaining 16 patients has not detected any ADRs.

As per demographic details of patients, there were 19 males (63%) and 11 females (37%). The age distribution data shows that most of patients are above age 65 the age distribution survey of 30 patients found that age group 21-40 has 20%, 41-60 has 36.66% and greater than 60 age group has 43.33% distribution. The distribution of patients of age group 0-20 has not accounted

From collected data, the more frequently detected ADR was bloating and indigestion almost 5 patients reported this. Apart from this gastric irritation and loss of appetite is frequently reported ADR of Metformin. Decrease level of vitamin b12, weakness, muscle pain, hypoglycaemia are also detected ADRs of Metformin. The organ system which is mostly affected with administration of Metformin is found to be a gastrointestinal system. Almost there are 10 ADRs are related with gastrointestinal system.

In order to strengthen and further emphasize the validity of the study, causality assessment was done using Naranjo scale. The assessment shows out of 19 ADRs 6 ADRs were probable and 1 is possible ADR. Probable ADRs includes, bloating, indigestion, gastric irritation, hypoglycaemia, loss of appetite, decrease level of vit b12 and abdominal pain was possible ADR associated with Metformin.

On evaluation of severity of ADRs by Hartwig and Seigel severity assessment scale, among 19 ADRs 16 ADRs are mild and 3 ADRs are moderate. Mild ADRs include weakness, loss of appetite, bloating indigestion. Moderate ADRs are decreased vit b12, gastric irritation, hypoglycaemia. No lethal ADRs were observed. As we considered gender distribution of ADRs most of ADRs are observed in males as there are more male patients in survey. There are more female patients who detected by mild ADRs than male patients. However, this particular no. Of data cannot predict exact and appropriate conclusion about sex distribution in ADRs associated with Metformin. The result can vary upon the survey and no. Of patients studied. Assessment of the preventability of the ADRs using modified Schumock and Thornton scale revealed that more of ADRs were probably preventable.

**4. 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.

In diabetic treatment the most commonly prescribed drug is Metformin. The above study shows that the ADRs associated with Metformin are probable. The severity of ADRs is mild to moderate. And the ADRs are probably preventable. Hence it can be concluded that among all the available anti diabetic drugs in market Metformin is most safest and effective drug in treatment of diabetes

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