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Research Article

Monitoring of adverse drug reactions in individuals with type II diabetes mellitus receiving oral hypoglycemic agents

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ABSTRACT

BACKGROUND: This study intends to ascertain the prevalence and overall burden of various adverse drug reactions (ADRs) driven by oral antidiabetics for treating type II diabetes mellitus (T2DM) in India.

METHODS: Patients with T2DM taking oral antidiabetic medications participated in prospective observational research. Data collection used the pretested format by the Indian pharmacovigilance program to record the history of drugs suspected to be responsible for ADRs. The causality evaluation is according to the guidelines of the Uppsala Monitoring Center and the World Health Organization.

RESULTS: This study included 424 patients with established diabetes. Female patients showed a non-significant higher percentage of ADRs (p = 0.059). Naranjo's assessment recorded 51 suspected ADRs with significant (p = 0.042) categorical differences in casualty. According to ADR severity, there was a significant (p = 0.048) difference between moderate 8.25% (n = 35) and mild 3.80% (n = 16); however, none of the ADRs showed severity. Metformin caused abdominal discomfort, itching, and rashes, accounting for 4.95% (n = 21) of all reported adverse reactions. Gliclazide and glimepiride induced hypoglycemia, itch, and rashes, 1.65% (n = 7), abdominal pain, 1.18% (n = 5), flatulence caused by acarbose, abdominal discomfort caused by pioglitazone, and pedal edema caused by pioglitazone 1.18% (n = 5).

CONCLUSION: ADRs due to oral antidiabetic agents are a frequent problem. Therefore, active pharmacovigilance is essential for risk identification, management, and establishing a robust antidiabetic drug ADR database.

1. INTRODUCTION

The statement that "no medicine is completely free of side effects" is universally accepted. According to the literature, 5 percent of all hospital admissions are due to drug-related complications, with 10-20 percent of hospitalized patients experiencing adverse drug reactions (ADR) (Kin *et al.*, 2011; James *et al.*, 1965). ADRs are believed to be the fourth to the sixth leading cause of death and were first recognized as an inadvertent or intentional medication error (Vargesson *et al.*, 2015; Edwards *et al.*, 2000; Kshirsagar *et al.*, 1993). ADR is a negative response to a drug at any clinical dose for treatment, prevention, or diagnosis, according to the World Health Organization (WHO) (Fornasier *et al.*, 2018; World Health Organization 2004). Therapeutic failures, intentional and unintentional poisonings, and drug abuse do not fall under this definition (World Health Organization 1972). According to the WHO Uppsala Monitoring Center (WHO-UMC), an ADR is "a substantial harmful or unpleasant reaction resulting from an intervention associated with the use of a pharmaceutical product, which predicts danger from future administration and demands prevention or particular treatment, or a change in the dose regimen, or a withdrawal of the product" (World Health Organization 1972; Tangiisuran *et al.*, 2012; Smyth *et al.*, 2014).

ADRs are more prevalent with multiple drug therapy, and the risk of an ADR incident increases for each new prescription given to a patient (Smyth *et al.*, 2014). ADRs can lead to decreased quality of life and increased medical care, admissions, and even death. Furthermore, they result in more significant healthcare expenses, and as a

result, they exert a significant strain on healthcare resources. The 1960s thalidomide tragedy was the darkest period in drug research (Kim *et al.,* 2011; James *et al.,* 1965). This disaster drew global attention to patient safety and emphasized the necessity for routine drug monitoring for "early warning system" adverse drug reactions (ADR) (Edwards *et al.,* 2000). Therefore, drug safety monitoring is an integral part of the healthcare system for providing high-quality medical care.

The WHO defines pharmacovigilance as the science and activities of assessing, detecting, understanding, and preventing adverse drug reactions (ADRs) and associated medical consequences (World Health Organization 1972). The overall goal of pharmacovigilance is to improve the safety of medicines intended for human use. Pharmacovigilance is a never-ending, evolving program in India that will be enhanced soon. As more and more prescription medications enter the Indian market, the demand for ADR monitoring is more significant than ever. As a result, side effects, particularly those of a severe magnitude, require treatment and hospitalization and must be monitored (Stålhammar *et al.,* 2001). Many ADRs can be reduced or eliminated by discontinuing the offending substance or reducing the dose, however, many others result in long-term harm. Hence it is compulsory to ensure the safety of the patients and drug use (Stålhammar *et al.,* 2001; Passarelli *et al.,* 2005; Sikdar *et al.,* 2012).

Healthcare providers must be motivated to recognize, manage, document, and report all ADRs and essential activities to maximize patient safety. In this study, we aimed to improve adherence to reporting cultures among healthcare providers and to monitor adverse drug reactions (ADRs) caused by oral hypoglycemic medications in patients with type II diabetes mellitus.

2. MATERIALS AND METHODS

2.1. Study design

This was a cross-sectional and observational study conducted in a prospective way in the University Hospital's outpatient department (OPD) of Singhania University (India). From June 2018 to May 2019, all type II diabetic adults taking oral hypoglycemic agents at the hospital and willing to provide a medical history were included in the study. The University Human Research Ethics Committee (HREC) received the protocol and the Informed Consent Form (ICF). The university ethics committee endorsed the project via letter no.: SU/HREC/2018/0509 for the conduct of this study. According to the Pharmacovigilance Programme of India (PPI), an ADR report form was prescribed for patients to submit under specific conditions. Good Clinical Practice (GCP) and the Declaration of Helsinki were adopted for the study.

2.2. Sample size calculation and sampling procedures

The sample size calculation is based on observational studies of the infinite population (Sharma *et al.*, 2019; Pourhoseingholi *et al.,* 2013).

The sample size of an infinite population is:

$$n_0 = \frac{z^2 pq}{e^2}$$

Where *e* is the precision (the desired degree of accuracy), q is $1 - p$ where p represents the estimated population proportion.

Therefore, for $p = 0.5$, a 95% confidence interval (CI), with an accuracy ± 5% Z values of 1.96 are obtained using the standard tables, we get a sample size:

$$n_0 = \frac{(1.96)^2 * (0.5) * (1 - 0.5)}{(0.05)^2}$$

$$n_0 = 385$$

We obtained 95% confidence intervals using a random sample of 385 participants from our target population. The sample was further inflated, considering the ten percent dropouts from the study:

Sample size (n) = 385 + 39
= 424

2.3. Subject selection

2.3.1 Inclusion criteria
Patients with existing T2DM or newly diagnosed over the age of 18 are taking at least one oral antidiabetic medicine.

2.3.2 Exclusion criteria
Diabetic individuals who are not on oral antidiabetic medications or on insulin. The study did not include patients under 18 or those abusing illicit or herbal medications.

2.4. Assessment of diabetes

For the oral glucose tolerance test (OGTT), blood samples from the patients were taken, and samples were transferred to the local pathology lab. The clinician interpreted the OGTT test results by the WHO guideline (1999) (World Health Organization 1999), which stated that impaired glucose tolerance was defined as fasting blood glucose levels between 110 and 125 mg/dl and blood glucose levels between 140 and 200 mg/dl after receiving 75 g of glucose orally. When the blood glucose levels at fasting and two hours after meals were observed to be higher than 125 mg/dl and 200 mg/dl, respectively, the individuals were claimed to have diabetes.

2.5. Sample and eligibility

A prospective inclusion in the study was determined for the T2DM patients who were on oral antidiabetic or started medications attending the clinic. They were screened according to the predetermined inclusion and exclusion criteria of the study. The participants were asked to follow up at least once a month and describe any adverse effects that they experienced. They were

clinically screened and adequately investigated for any ADRs.

2.6. Data collection

Clinical records were used to extract data on gender, weight, age, height, waist-to-hip ratio (WHR), BMI, HbA1c levels, blood sugar, prescribed medications, and dietary and exercise recommendations. Clinical judgment is the basis for estimating the probability that a drug causes an adverse reaction. Assessing the precise nature of an ADR results in significant diversity when using the traditional categories and criteria of definite, probable, potential, and questionable ADRs.

2.7. Assessment of ADRs

ADRs are classified using the WHO-UMC scale based on the timing association with drug consumption, the administration of any other treatments, and the response to challenge– dechallenge–rechallenge (CDR). ADRs are categorized as "unlike", "probable", "possible", and "certain" based on the risk scale. While the Naranjo scale is based on a 10 questions survey with a score of +2, +1, 0, or -1 for each question. The total score is ≥ 9 labeled as definite, 5-8 probable, 1-4 is possible, and ≤ 0 is doubtful/unlikely (Table 1). ADRs are divided into three categories: mild (annoying but not necessitating a modification in therapies), moderate (therapy modification is necessary, additional care and/or hospitalization), and serious (life-threatening, disabling, treatment and hospitalization needed) (Kaur *et al.*, 2011). The Modified Hartwig and Siegel's scale was used to assess the severity and to determine causality according to Naranjo's scale (Naranjo *et al.*, 1981; Hartwig *et al.*, 1992).

2.8. Statistics

Performing data analyses using the statistical analysis software (SPSS) package 23.0. For categorical variables, the frequency and percentages were shown. Descriptive statistics of categorical data were used to estimate the prevalence of ADR. Mean ± SEM presented quantitative data. The level of statistical significance was defined as $p \leq 0.05$.

3. RESULTS

3.1. Patient demographic characteristics

During the one-year study period, 424 patients with established T2DM attended the hospital, with (n = 187; 44.03%) males and (n = 237; 55.97%) females. The patients in the study had an average age of 51.4 ± 12.2 years. The studied population's average body mass index (BMI) was 25.2 ± 4.2 kg/m^2. BMI >23 kg/m^2 was found in 71.2% of the study group. In the female population, the mean waist-hip ratio (WHR) was 0.87 ± 0.035, whereas, in the male population, it was 0.89 ± 0.031. Female subjects had a waist circumference of 83.46 ± 8.5 cm, whereas male individuals had a waist circumference of 85.13 ± 7.39 cm. 27.2% of the patients had a positive diabetic family history. Education status reported none/nil 40.8% while only 3.6% were postgraduates. Housewives were in the highest presentation with 49.5% while the least presentation of retired 9.30%. T2DM patients had a history of diabetes dating back 2-5 years, while 14.1% had a 5-10-year-old history. Non-vegetarian patients comprised 79.9% of the total T2DM patients (Table 2). Female patients had a slightly higher rate of adverse drug reactions caused by oral hypoglycemic agents (Table 3).

3.2. ADRs with the oral hypoglycemic agents

Insulin and metformin had the highest number of ADRs recorded. All nine ADRs with insulin were hypoglycemia, with three being highly likely and necessitating hospitalization. Metformin was associated with a higher rate of abdominal discomfort (possible). Hypoglycemia was the most prevalent ADR among type II diabetes patients.

Table 1: Naranjo's adverse drug reaction probability scale.

	Assessment	Yes	No	Do not know	Score
1.	Are there previous conclusive reports on this reaction?	+1	0	0	
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3.	Did the adverse event improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	
4.	Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total Score					

Table 2: Patient sociodemographic characteristics.

Characteristics	Gender	Distribution n (%)
Gender	Males	187 (44.03)
	Females	237 (55.97)
Mean Age		51.4 ± 12.2 years
Mean BMI		25.2 ± 4.2 kg/m^2
		71.2% had BMI > 23 kg/m^2
Mean WHR	Females	0.87 ± 0.035
	Males	0.89 ± 0.031
Waist circumference (cm)	Females	83.46 ± 8.5
	Males	85.13 ± 7.39
Family history		27.2%
Dietary habits	Vegetarian	20.1%
	Non-vegetarian	79.9%
Education	Nil	40.8%
	Less than high school	11.4%
	High school	13.7%
	Intermediate	11.4%
	Graduate	18.8%
	Postgraduate	3.6%
Work status	Employed	15.80%
	Business	17.40%
	Retired	9.30%
	Housewives	49.50%
	Unemployed	8.10%
Years of diabetes	New	2.7%
	< 6 months	9.8%
	6 months – 1 year	10.3%
	2 - 5 years	50.5%
	5 - 10 years	14.1%
	10 - 15 years	9.2%
	15 - 20 years	2.7%
	>20 years	0.5%

The ADRs with metformin were itching, rashes, and abdominal discomfort (Table 4).

Table 3: Gender distribution (ADR).

Gender	Total number of ADRs n (%)
Male	21 (4.95)
Female	30 (7.08)
Total	51 (12.03)

3.3. Classification of ADRs

There was a non-significant difference in gender (p = 0.059) with a higher percentage of female patients experiencing ADR. According to Naranjo's scale, a significant number of ADRs (p = 0.042) were found to be unlike 1.18% (n = 5), possible at 9.2% (n = 39), followed by 1.65% (n = 7) probable. Significantly (p = 0.048) a higher number of ADRs were observed, moderate 8.25% (n = 35) than mild 3.8% (n = 16), which included mainly hypoglycemia due to oral hypoglycemic agents (Table 5).

3.4 Increased risk of adverse drug reactions with concomitant drugs

There were 424 patients with type II diabetes, and 18 (4.25%) were taking medication that would have intensified the effects of oral hypoglycemic medications (enalapril, diclofenac). Five patients (1.18%) were being treated with medicines known to reduce the effects of oral hypoglycemic agents (hydrochlorothiazide). Thirty-six peoples (8.5%) took medicines known to induce hyperglycemia (frusemide, hydrochlorothiazide).

Table 4: Adverse drug reactions recorded with different oral hypoglycemic agents and casualty assessment.

Suspected drugs	ADR experienced	No. of ADRs	% of ADRs	Interventions	Causality Assessment
Sulfonylureas					
Glimepiride	Abdominal pain	5	1.18	Symptomatic treatment	Unlikely
Glipizide	Hypoglycemia	2	0.471	Dechallenged and glimepiride was added	Probable
Gliclazide	Itching, rashes	5	1.18	Symptomatic treatment	Possible
	Hypoglycemia	2	0.471	Dechallenged and changed to glimepiride	Probable
Total		**14**	**3.3**		
Biguanides					
Metformin	Itching, rashes	7	1.65	Symptomatic treatment	Possible
	Abdominal discomfort	14	3.3	Symptomatic treatment	Possible
Total		**21**	**4.95**		
Thiazolidinediones					
Pioglitazone	Pedal edema	**5**	**1.18**	None	Possible
Alpha-Glucosidase inhibitors					
Voglibose	Flatulence, Abdominal discomfort	2	0.471	Symptomatic treatment	Possible
Miglitol	Abdominal pain	2	0.471	Symptomatic treatment	Possible
Acarbose	Flatulence, Abdominal discomfort	5	1.18	Symptomatic treatment	Possible
Total		**9**	**2.12**		
DPP4 Inhibitor Vildagliptin	Headache dizziness	**2**	**0.471**	Symptomatic treatment	Possible
Grand total		**51**	**12.03**		

4. DISCUSSION

The pharmacovigilance program aims to identify ADRs in a large population, identify new and uncommon ADRs, track their frequency, and put prevention strategies in place. An essential approach for describing drug incidents is spontaneous and voluntary reporting. However, its benefits and shortcomings have been extensively studied (Griffin *et al.,* 1985). Following the principle of universal compliance, the system has been adopted and implemented in many nations, including India. In the last few years, many newer antidiabetics have been introduced in the market, but in the Indian market, their safety data is limited. Through spontaneous or requested ADR monitoring, the current study actively collected data. This study aimed to understand the safety profile of currently prescribed oral antidiabetic medications among people with type II diabetes. Type II diabetes was identified in a total of 424 subjects. Throughout the investigation, diabetic individuals were monitored for adverse events. Unscheduled reports of ADRs are also included in the examination.

The total number of female patients was higher than the male thus predominance can be seen in this study. This study is similar to studies available

Table 5: Gender distribution of ADR and grading on severity and Naranjo scale (n = 51).

	Categorical measures		**ADRs n (%)**	***p***
Gender	Male		21 (4.95)	0.059
	Female		30 (7.08)	
		Score		
Naranjo's scale	Unlike	≤ 0	5 (1.18)	0.042
	Possible	1-4	39 (9.2)	
	Probable	5-8	7 (1.65)	
	Highly probable	≥9	0(0)	
Severity	Mild		16 (3.80)	0.048
	Moderate		35 (8.25)	
	Severe		0 (0)	

(Stålhammar *et al.,* 2001; Singh *et al.,* 2017) but different from the study reported in the literature (Chiang *et al*., 2006; Yusefzadeh *et al.,* 2014). Study participants had an average BMI of more than 23 kg/m^2. Female diabetic patients had WHR significantly higher than the permitted limit of 0.85. As a result, a significant number of female diabetic patients had WHR higher than average. Moreover, female subjects had a larger mean waist circumference than usual, and their waist circumference exceeded acceptable limits. The female dominance in participants might be due to excessive body weight (high BMI), working style, and less physical activities because the highest numbers of female patients were housewives.

Assessment of adverse drug reactions aids in understanding the relationship between a drug's adverse effects, severity, and preventability. Patient compliance may be improved as a result of feeling more confident. A total of 51 (12.03%) ADRs were reported in this study. Most patients experiencing ADRs were females (30 out of 51). This study observed that metformin (Stålhammar *et al.,* 2001) is associated with the highest number of ADRs, followed by gliclazide, glimepiride, pioglitazone, and vildagliptin. The most common ADR among T2DM patients on oral hypoglycemic agents was abdominal discomfort followed by itch and rashes. The overall incidence of abdominal discomfort was 6.5%, with the maximum incidence caused by biguanide (metformin) being 3.3%. Huang *et al*. 2020 also reported a similar pattern to the present study (Huang *et al.,* 2020). The increased rate of ADR could be due to pharmaceutical or non-pharmaceutical. Inappropriate drug administration, patient noncompliance, inappropriate instructions followed, or inappropriate food intake may also contribute to ADRs (Shanthi *et al.,* 2018).

In this study, the highest number of ADRs for casualty assessment on Naranjo scale were reported as possible (n = 39) and unlike with least number (n = 5) while highly probable ADRs were nor reported this study provides similar data as reported by Stålhammar *et al*. (Stålhammar *et al.,* 2001). A study conducted in a secondary care hospital reported 73.33% of ADRs categorised as possibly which was higher than our study (Arulmani *et al.,* 2008). On severity scale of assesment no severe reactions were observed while moderate were documented in highest percentage (n = 35) but mild were 3.8% (n = 16). These results agree with previous studies and supports the present study findings (Stålhammar *et al.,* 2001; Chiang *et al.,* 2006; Bell *et al.,* 2006; Al-Abri *et al.,* 2013).

5. CONCLUSION AND RECOMMENDATION

Overall, oral antidiabetic medicines seem to be safe, but they do have the potential to induce adverse reactions. The most common ADRs were gastrointestinal, musculoskeletal, and metabolic disorders. Most ADRs were associated with metformin (biguanide) and gliclazide (sulphonylureas). ADR monitoring is required due to the introduction of a substantial number of novel oral antidiabetic drugs to the market and prescription. As a result, active pharmacovigilance should be used to identify and control risks.

In developing nations like India, where the population is relatively high, pharmacovigilance in the post-marketing phase should be promoted and supported so that a significant number of adverse drug reactions (ADRs) related to prescribed pharmaceuticals are recorded and prevented in the future. Patients using insulin and other oral hypoglycemics may benefit from patient education and counseling to lower the risk of hypoglycemia crises. For better patient care, counseling should be emphasized in hospitals and community pharmacies.

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