

# Adverse drug reactions in Type 2 diabetes mellitus patients on oral antidiabetic drugs in a diabetes outpatient department of a tertiary care teaching hospital in the Eastern India

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Received: April 26, 2016; Accepted: October 03, 2016

## ABSTRACT

**Background:** Diabetes mellitus is a major healthcare problem in India. Pharmacovigilance of antidiabetic drugs is crucial in detecting adverse drug reactions (ADRs) and providing feedback to physicians on their possibility. In India, few reports are available on the ADR profile of antidiabetic agents. **Objectives:** This study aims to detect frequency and total burden of different ADRs due to oral antidiabetic drug (OAD) use in a diabetes outpatient in a medical college in Eastern India. **Materials and Methods:** An observational study was conducted on Type 2 diabetes mellitus patients on oral antidiabetic agents, attending Diabetes Clinic of a Tertiary Care Teaching Hospital in West Bengal between April and September 2013. Details of adverse event history, history of medication suspected of having caused the ADR were recorded in the format followed in the Pharmacovigilance Programme of India. The causality relationship was assessed by the World Health Organization-Uppsala Monitoring Centre criteria. **Results:** A total of 1000 patients were screened, of which 276 were suspected of having at least one ADR. On causality assessment, 43 of these 276 cases had insufficient evidence about causality and were excluded from the analysis. Out of the remaining 233 patients, 275 suspected ADRs were detected. Among them, metformin contributed 51% of total ADR reported, in the form of dyspepsia and diarrhea, followed by glimepiride-induced hypoglycemia. Voglibose-induced dyspepsia, pioglitazone-induced pedal edema were also common. **Conclusions:** ADRs due to OADs is a frequent problem. Few multicentric studies are needed for a strong antidiabetic drug ADR database in India.

**KEY WORDS:** Adverse Drug Reactions; Type 2 Diabetes Mellitus; Oral Antidiabetic Drugs; Outpatient Department; Eastern India


## INTRODUCTION

Diabetes mellitus has emerged as a major healthcare problem in India. According to estimates, India has the highest number of adults with diabetes reported at 50.8 millions in 2010 which

is expected to rise to 87 millions by 2030.<sup>[1]</sup> The prevalence of diabetes has been reported to be rapidly increasing in both rural and urban India.<sup>[2]</sup>

An oral antidiabetic drug (OAD) is the first line of drug treatment for Type 2 diabetes. However, the progressive nature of Type 2 diabetes usually requires a combination of two or more oral agents in the long term. Safety and tolerability often limit the optimal use of OADs.<sup>[3]</sup>

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is defined as “a noxious, unintended, and undesirable effect that occurs as a result

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Website: <a href="http://www.ijmsph.com">http://www.ijmsph.com</a>	Quick Response code
DOI: 10.5455/ijmsph.2017.0423203102016	

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of dose normally used in man for diagnosis, prophylaxis, and treatment of disease or modification of physiological function.”<sup>[4]</sup> A number of factors are in general responsible for ADRs including polypharmacy, drug interactions, and complexity of diseases.

Pharmacovigilance of antidiabetic drugs can play a crucial role in detecting ADRs and providing feedback to physicians on the possibility and details of such events, thereby protecting the patients from avoidable harm.<sup>[5]</sup> In India, pharmacovigilance activities are still in nascent stage and initiatives are being taken for spontaneous ADR reporting under the Pharmacovigilance Programme of India. However, in India, there are very few reports available on the ADR profile of antidiabetic agents in particular. Hence, this study aims to detect frequency and total burden of different adverse events due to OAD use in a diabetes outpatient department (OPD) of a medical college in Eastern India.

## MATERIALS AND METHODS

A longitudinal observational study was conducted on Type 2 diabetes mellitus patients on oral hypoglycemic agents, attending Diabetes Clinic of College of Medicine and JNM Hospital, Kalyani, a tertiary care teaching hospital in West Bengal between April and September 2013. Patients receiving Insulin were excluded from the study.

All suspected ADRs were initially assessed by the Consultant Incharge - Diabetes Clinic and subsequently the information was collected and analyzed by the pharmacologists for causality assessment.

Patient details (age, sex, body weight), adverse event history, history of medication suspected of having caused the ADR, including its onset, duration, temporal association with drug intake if any and details of concomitant medication use, were recorded in the format followed in the Pharmacovigilance Programme of India.<sup>[6]</sup>

The causality relationship among ADR and drug was assessed by the WHO-Uppsala Monitoring Centre (WHO-UMC) criteria.<sup>[7]</sup>

Suspected ADRs with causality status less than “possible” were not analyzed further.

## RESULTS

A total of 1000 patients were screened for the study, of which 276 (27.6%) were suspected of having at least one ADR from oral hypoglycemic agents. On causality assessment, 43 of these 276 cases (16.66%) were considered to have insufficient evidence about causality (WHO-UMC causality

status “unlikely”), and they were excluded from further analysis. Out of the remaining 233 patients analyzed, 275 suspected ADRs were detected. Few patients had reported the presence of more than one ADR, either due to single drug use or due to multiple antidiabetic drug use. Thus, 23.30% (233) of our total subjects (1000) reported ADRs with at least “Possible” Causality.

No ADR encountered turned out to be fatal, life-threatening, or required hospitalization for management. None of the ADRs was labeled “Certain” as rechallenge in the same dose, was not attempted by the attending physician, once a drug was withdrawn.

Out of 1000 patients, 562 were male, and 438 were female. The average age of the patients were 48.32 among 233 patients, who had ADR, 129 patients were male, and 104 were female. Percentage of ADR occurrence among all male patient was 22.95%, and among female, it was 23.74%.

Out of 1000 patients, 963 patients were given metformin; dose varied from 500 mg/day up to 2 g/day. Out of them, total 108 patients (11.21%) reported one or more adverse effect after use of this drug. Among them, there were 84 incidents of dyspepsia, 49 incidents of diarrhea, and 9 incidents of nausea, vomiting (Table 1).

A total of 628 patients were given glimepiride in the study group; dose varied from 1 to 4 mg/day. Among them, 74 patients had some symptoms of hypoglycemia (sweating, tremor, palpitation, vertigo, and dizziness) and 6 patients complained about weight gain after the use of glimepiride. Hence, total 80 patients (12.74%) had some adverse event due to glimepiride use (Table 2).

A total of 67 patients were given voglibose for controlling postprandial hyperglycemia. Among them, 32 patients (47.76%) reported to have dyspepsia. 8 patients among those also had diarrhea.

Pioglitazone was given in 71 patients. 13 of them (18.31%) had complained about pedal edema. All of them occurred in the dose of 15 mg/day (Figure 1).

## DISCUSSION

The present study has reported the incidence and attempted to profile suspected ADRs due to antidiabetic drugs in the diabetes OPD setting in the Indian context. In contrast to reports of ADR profiles of individual drugs, there is a dearth of pharmacovigilance profiling of antidiabetic agents in general in India, that too, keeping insulin out of the list. Hypoglycemia due to insulin is the most common adverse event reported in most of the drug utilization studies,<sup>[8]</sup> but our study aims for the common adverse events due to OADs

**Table 1:** Frequency of different adverse effects with different drug use

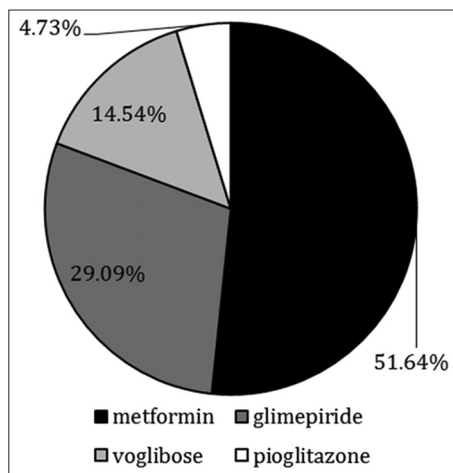
Name of the drugs	Number of patients given (out of 1000)	Number of patients reported ADR	Percentage of ADR occurrence among users	Nature of ADR	Total ADR reported due to individual drug
Metformin	963	108	11.21	Dyspepsia (84), diarrhea (49), nausea, vomiting (9)	142
Glimepiride	628	80	12.74	Hypoglycemic symptoms (74), weight gain (6)	80
Voglibose	67	32	47.76	Dyspepsia (32), diarrhea (8)	40
Pioglitazone	71	13	18.31	Pedal edema (13)	13

ADR: Adverse drug reactions

**Table 2:** Contribution of different drugs in overall ADR occurrence (due to OADs)

Suspected drug	Number of suspected ADR	Percentage of total ADR, contributed by the drug (n=275)
Metformin	142	51.64
Glimepiride	80	29.09
Voglibose	40	14.54
Pioglitazone	13	4.73

ADR: Adverse drug reactions, OAD: Oral antidiabetic drug



**Figure 1:** Percentage of adverse drug reactions due to oral antidiabetics, contributed by different drugs

only. Hence, it had dyspepsia as the most common ADR, not hypoglycemia.

In a study conducted in Italy,<sup>[9]</sup> Overall 148,289 ADR reports have been collected and, of these, 3416 (2.3%) were due to antidiabetic agents. The most reported serious ADRs were severe hypoglycemia (about 50% of serious ADR reports), mainly caused by insulins or sulfonylureas, lactic acidosis from metformin, pancreatitis from incretins.

In that study, reported ADRs for sulfonylureas and biguanides were mainly metabolic disorders. Regarding alpha-glucosidase inhibitors, glucagon-like peptide-1 mimetics and dipeptidyl peptidase-4 (DPP-4) inhibitors, gastrointestinal system was the most frequently affected site.

In our study also, dyspepsia and diarrhea were the most common adverse effect reported by patient to doctors, mostly due to metformin, followed by voglibose.

Glimepiride alone or its combination with metformin caused a few incidence of hypoglycemia, all of them have occurred if glimepiride was used with dose of 2 mg/day or more.

Metformin-induced dyspepsia occurred only if it was used in dose more than 1000 mg/day.

Incidence of dyspepsia was also common with use of voglibose, as expected from its mechanism of action. Metformin with voglibose combination produced more frequent incidents of dyspepsia.

This study have found a few cases of pedal edema with pioglitazone use, in dose of 15 mg. Higher than 15 mg dose for pioglitazone was not used. The patients who reported edema, their dose for pioglitazone was reduced to 7.5 mg/day, which did not produce pedal edema to any of the subjects.

As obtained from the vigiflow data from India,<sup>[10]</sup> in the period 2010-2012, 466 cases of adverse events due to antidiabetics were reported. Average onset age (mean±standard error of mean) of male patients was 51.0 ± 0.72 and female patients 50.433 ± 0.72. It was found that 40% of ADR related to antidiabetics were occurred in female, whereas 60% in counterpart. 26% cases were found to be of the serious, Metabolic and nutritional disorders constituted 13%, gastrointestinal system disorders constituted 5% and central nervous system disorders constituted 4%. Two cases of hypoglycemia were responsible for the life-threatening condition during this period. One case of metformin-induced encephalopathy without metabolic syndrome was found which is the unexpected. In most of the cases, reporter was doctor.

In our study, out of 233 ADRs, 129 were reported by male and 104 were reported by female patients. There were no serious events recorded, may be due to insulin was kept out of the measurement, which is the most common agent to cause fatal hypoglycemia.

Most of the adverse effects were managed by reducing the dose of the drug, and in some cases by stopping the drug such as stopping glimepiride if patient had prolonged hypoglycemia.

DPP 4 inhibitors use did not produce any adverse events, may be due to their use was restricted to a small number of patients, as high cost of these drugs is a constraint for use in relatively poor Indian patients.

Our study had limitations. For logistical reasons, we screened patients on one fixed day of each week, and this could introduce potential bias in the sample. Being an OPD-based study, it is likely that we have missed ADRs that were transient or too mild to motivate the patient to report to the doctor on the next hospital visit.

ADRs can perhaps also be reduced using less medication and with adequate knowledge of drug interactions.<sup>[11]</sup> An antidiabetic drug ADR database built up on the basis of such studies conducted across multiple centers, through active collaboration of diabetologists and pharmacologists, can be a worthy long-term goal in the Indian context.

**CONCLUSIONS**

ADRs due to OAD is a very frequent problem. Although they are not likely to be life-threatening, but they can cause various types of discomforts in many patients. Few large multicentric studies on this matter need to be done to build a strong antidiabetic drug ADR database.

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**How to cite this article:** Deb T, Chakrabarty A, Ghosh A. Adverse drug reactions in Type 2 diabetes mellitus patients on oral antidiabetic drugs in a diabetes outpatient department of a tertiary care teaching hospital in Eastern India. *Int J Med Sci Public Health* 2017;6(3):554-557.

**Source of Support:** Nil, **Conflict of Interest:** None declared.