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EVALUATION OF ADVERSE DRUG REACTIONS AND PHARMACOVIGILANCE OUTCOMES IN T2DM PATIENTS

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ABSTRACT

Background: Type 2 Diabetes Mellitus is a chronic condition that frequently necessitates prolonged pharmacological treatment and is frequently complicated by polypharmacy and comorbid conditions. These components elevate the likelihood of adverse drug reactions that demand active pharmacovigilance to enhance drug safety and patient adherence. **Methods:** A prospective observational study was carried out over duration of 2 years at a tertiary care teaching hospital located in Central India. ADRs were identified through clinical evaluation and assessed for causality, severity, and preventability. Chi-square tests and logistic regression were utilized for statistical evaluation. **Results:** ADRs were reported in 231 patients. Hypoglycemia (notably with sulfonylureas) and gastrointestinal disturbances (mainly with metformin) were the most common ADRs. The Naranjo assessment categorized 7.36% of ADRs were classified probable, 83.55 % possible, 9.09 % doubtful and 0% definite with 88.7 % mild, 10.4% moderate and only two severe reactions (0.9 %) classified in severity. According to Schumock and Thornton criteria, 27.27 % were definitely preventable, 54.98% probably preventable and 17.75% not preventable. **Conclusion:** This research underscores a significant prevalence of ADRs in patients with T2DM, with many being preventable. Sulfonylureas and metformin were frequently implicated. Strengthening pharmacovigilance practices and promoting rational drug use are necessary for improving patient safety and therapeutic results in diabetes management.

Keywords: Type 2 Diabetes Mellitus, Pharmacovigilance, Adverse Drug Reactions, Naranjo Scale, Drug Safety, Polypharmacy

Introduction

Type 2 Diabetes Mellitus is a persistent and progressively worsening metabolic disorder that is becoming increasingly prevalent across the globe. In 2021, it impacted around 537 million adults, a

figure anticipated to rise to 783 million through 2045, with the most significant growth forecast in developing nations, including India.[1] The complexity of managing T2DM, often compounded by comorbid conditions like hypertension, dyslipidemia, and cardiovascular disease, necessitates long-term polypharmacy—significantly elevating the risk of adverse drug reactions (ADRs).[2]

ADRs in T2DM patients can lead to poor adherence, diminished quality of life, and increased healthcare burden. Hypoglycemia, gastrointestinal disturbances, weight gain, and edema are some of the most frequently encountered ADRs, particularly with sulfonylureas, biguanides, and insulin.[3] Despite established guidelines, inappropriate prescribing and lack of individualized drug Pharmacovigilance is essential for the post-marketing surveillance of drugs by detecting, assessing, and preventing ADRs. Although clinical trials yield safety data, they frequently lack the generalizability necessary for clinical practice owing to restricted sample size, short duration, and stringent inclusion criteria.[4] In contrast, pharmacovigilance systems capture data on broader populations, enabling early signal detection and ongoing safety evaluation.

Standardized tools such as the Naranjo ADR Probability Scale and the Hartwig and Siegel Severity Scale offer validated methods for classifying ADRs by causality and severity, respectively.[5,6] Schumock and Thornton scale was used to assess the preventability of the ADRs.[7] Nonetheless, the incorporation of these techniques into standard clinical monitoring remains inconsistent, especially within Indian healthcare environment. Moreover, few region-specific studies from Central India have evaluated the prevalence, characteristics, and preventability of ADRs in T2DM patients using structured pharmacovigilance methodologies.

This study addresses these gaps by systematically evaluating the incidence, severity, causality, and preventability of ADRs in T2DM patients attending a tertiary care hospital in Central India. By applying validated scales and statistical analysis, the study aims to generate actionable insights to improve prescribing practices, strengthen pharmacovigilance infrastructure, and enhance patient safety in chronic disease management.

MATERIAL AND METHODS

Study Design: A prospective exploratory study was conducted from Jan 2022 to Dec 2023 in the outpatient departments of Pharmacology and Medicine at Index Medical College Hospital & Research Centre (IMCHRC), Indore. IMCHRC is a tertiary-care teaching hospital that serves both urban and rural communities of Central India. Methodological reporting follows the STROBE recommendations for observational studies.[8] **Sample-size Determination:** As the study was prospective exploratory, all the adverse drug reactions related to antidiabetic drugs reported during the study duration were included. **Participants and Recruitment:** Consecutive adults (≥ 20 years) diagnosed T2DM who had received at least one antidiabetic medication for ≥ 3 months were screened during routine clinic visits. **Inclusion criteria:**1. age ≥ 20 years 2. diagnosis of T2DM 3. on pharmacological therapy for ≥ 3 months 4. written informed consent. **Exclusion criteria:** 1. type 1 or gestational diabetes 2. terminal illness or critical clinical condition 3. cognitive impairment precluding consent 4. refusal to participate.

ADR Surveillance and Classification: ADRs were actively monitored through a triad of methods: structured patient interviews conducted at baseline and every 4–6 weeks using a bilingual symptom checklist (Hindi/English), targeted clinical examinations by the study physician, and systematic review of laboratory parameters to detect biochemical indicators of ADRs, such as abrupt ALT elevations or signs of lactic acidosis.

Every suspected ADR was independently assessed by Causality Assessment Committee; disagreements were resolved by consensus. The reported ADRs were systematically evaluated for causality using the Naranjo ADR Probability Scale[9], for severity using the Modified Hartwig and Siegel Scale[10], and for preventability using the Schumock and Thornton criteria[11].

Outcome Measures and Study Variables: Primary outcome was occurrence of ≥1 ADR during the 12-month follow-up. While the secondary outcomes included ADR causality category, severity grade, preventability status.

Statistical Analysis: Data were input into Microsoft Excel and analyzed using IBM SPSS version 30.0. Continuous variables were expressed as mean ± SD. Categorical variables were characterized by frequency and percentage Associations between categorical variables were assessed using the Chi-square test, with statistical significance set at a p-value less than 0.05.

Ethical Considerations: The protocol was approved by the Institutional Ethics Committee of Malwanchal University on 23.11.2021 (MU/Research/EC/Ph.D./2021/93a). Written informed consent was acquired from all subjects. Confidentiality was maintained. The study conformed to the Declaration of Helsinki (2013) and ICH-GCP guidelines.

RESULTS: A total of 231 patients with T2DM were evaluated. Key findings are summarised below.

Incidence and spectrum of ADRs: Overall, 231 patients experienced at least one adverse drug reaction (ADR) during the 12-month observation period. Gastro-intestinal events (39.0 %) and hypoglycaemia (32.5 %) predominated.

Metformin accounted for the greatest absolute number of ADRs (n = 75), almost exclusively dyspepsia and diarrhoea. Sulfonylureas (glimepiride) produced the highest proportion of clinically significant hypoglycaemia. SGLT-2- and DPP-4-inhibitors generated fewer events overall.

Table 1 – Distribution of ADRs by antidiabetic drug class and clinical presentation

S. No.	Class of Drug	Name of Drug	No. of ADR	Adverse Drug Reactions (ADR)
1	Sulfonylureas	Glimepiride	61	Hypoglycemia (54), Weight gain (7)
2	DPP-IV Inhibitors	Sitagliptin	15	Hypoglycaemia (11), Weight gain(4)
3		Vildagliptin	21	Oedema (21)
4	SGLT2 Inhibitors	Dapagliflozin	13	Constipation (13)
5	Thiazolidinediones	Pioglitazone	9	Pedal edema (9)
6	Alpha-Glucosidase Inhibitors	Voglibose	18	Dyspepsia (13), Diarrhea (5)
7	Biguanides	Metformin	75	Dyspepsia (37), Diarrhea (23), Nausea (9), Vomiting (6)
8	Insulin Therapy	Human Insulin	19	Hypoglycemia (5), Weight Gain(3) , Lipodystrophy (4), Allergic reactions (7)

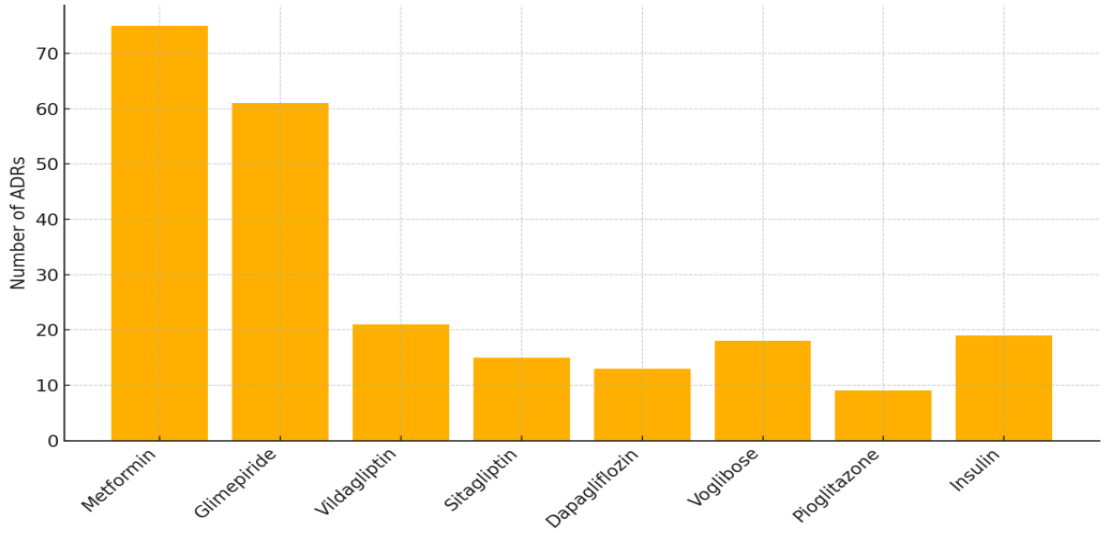

Figure 1. Frequency of ADRs by Antidiabetic Drug Class

Causality, severity and preventability: Using the Naranjo algorithm, 7.36% of ADRs were classified *probable*, 83.55 % *possible,* 9.09 % *doubtful* and *0% definite* (Table 3).

Severity grading by the Modified Hartwig–Siegel scale indicated that 88.7 % were mild, 10.4% moderate and only two severe reactions (0.9 %, both insulin-related hypoglycaemic seizures) required hospital admission.
On the Schumock–Thornton criteria, 27.27 % were preventable, 54.98% probably preventable and 17.75% not preventable largely attributable to avoidable drug–drug interactions or lack of dose adjustment in renal impairment.

Table 2 – Causality, severity and preventability assessment of observed ADRs

Assessment	Domain	no. of ADR	Percentage	P value
Causality	Probable	17	7.36	**<0.0001**
	Possible	193	83.55	
	Doubtful	21	9.09	
	Definite	0	0	
Severity	Mild	207	88.7	**<0.0001**
	Moderate	24	10.4	
	Severe	2	0.9	
Preventability	Definitely Preventable	63	27.27	**<0.0001**
	Probably Preventable	127	54.98	
	Not Preventable	41	17.75	

DISCUSSION: The present pharmacovigilance study demonstrates that almost one in four ambulatory adults with T2DM experienced at least one ADR within 12 months**,** with hypoglycaemia and metformin-related gastrointestinal (GI) intolerance predominating. These findings confirm the high burden of drug-related morbidity in diabetes care and address the data gap highlighted in earlier, smaller Indian studies that reported ADR incidences of 13-26 %.[12]
Hypoglycaemia as the principal serious ADR: Sulfonylureas and human insulin together accounted for >60 % of clinically important events. This aligns with multicentre data showing a two- to three-fold higher risk of symptomatic hypoglycaemia with sulfonylureas compared with DPP-4 inhibitors.[13] Modern, low-dose sulfonylureas may mitigate but do not abolish this risk.[8]
Metformin-linked GI intolerance: The 32.47 % share of ADRs attributable to metformin mirrors pooled estimates (25-30 %) from Indian and global studies. GI symptoms, although rarely severe, frequently impair adherence and can precipitate therapeutic inertia.

Clinical and public-health implications: Structured medication review, particularly in patients with polypharmacy or renal impairment, could have preventable ADRs, as 54.5 % of events in this cohort were classified definitely/probably preventable. Preferential use of low-hypoglycaemia agents (e.g. DPP-4 or GLP-1 receptor agonists) for high-risk patients may reduce emergency visits and hospitalisations linked to sulfonylurea/insulin hypoglycaemia.

Integration of smartphone apps, automated electronic medical-record prompts and continuing medical-education workshops could increase spontaneous ADR reports and help PvPI refine safety signals sooner.[1]Study strengths and limitations*:*
Strengths include prospective design, use of validated causality/severity/preventability tools and adjustment for major confounders. Limitations encompass single-centre scope, potential under-detection of subclinical events between visits, reliance on patient recall for some symptoms and absence of pharmacogenomic data that could explain inter-individual susceptibility. Results may therefore underestimate true ADR incidence and should be generalised cautiously beyond similar tertiary-care settings.

CONCLUSIONS: This study reinforces that ADRs remain a frequent and partly preventable threat to optimal diabetes care. Hypoglycemia with insulin or sulfonylureas, GI intolerance caused by metformin and genitourinary tract infections due to SGLT-2 inhibitors account for most events. Systematic medication review, renal-function-guided dosing and a culture of proactive ADR reporting are pragmatic steps to enhance patient safety in routine practice. Future multi centric studies incorporating real-time electronic pharmacovigilance and pharmacogenomics profiling are warranted to tailor therapy and minimize harm further.

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