

Global Adverse Event Reporting Patterns of Major Antidiabetic Drug Classes: A WHO-Vigi Access Analysis

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ABSTRACT

Antidiabetic medications are widely used for the management of diabetes mellitus but may be associated with a broad spectrum of adverse drug reactions (ADRs). Post-marketing pharmacovigilance is important for identifying patterns of adverse events that may not be fully characterized during pre-marketing clinical trials. This study aimed to describe global ADR reporting patterns associated with major antidiabetic drug classes using WHO-VigiAccess data. A cross-sectional, descriptive pharmacovigilance study was conducted using publicly accessible WHO-VigiAccess. Fourteen antidiabetic drugs belonging to five classes biguanides, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists were evaluated. ADR reports were analyzed descriptively according to drug, pharmacological class, geographical region, sex, age group, and MedDRA System Organ Class (SOC). A total of 759,284 ADR reports were analyzed. Metformin had the highest number of reports among individual drugs (203,073), while GLP-1 receptor agonists accounted for the largest proportion of reports by class (288,372; 37.98%). America, Asia, and Europe contributed the majority of reports, with marked geographical variation between individual drugs. ADR reporting was predominantly observed among patients aged 45–64 years, followed by older age groups. A slight overall male predominance was observed, although sex distribution varied between drugs. Gastrointestinal disorders were the most frequently reported ADR category, particularly with metformin and GLP-1 receptor agonists. Sulfonylureas showed prominent metabolism and nutrition-related events, while SGLT2 inhibitors were associated with higher reporting of infections and renal/urinary disorders. The study demonstrates substantial variation in global ADR reporting patterns among antidiabetic medications. The findings highlight the value of WHO-VigiAccess for identifying patterns of reported adverse events and emphasize the need for continued pharmacovigilance and further epidemiological studies. ADR reporting frequencies should not be interpreted as measures of incidence, causality, or comparative drug safety.

Keywords: Antidiabetic drugs; Adverse drug reactions; Pharmacovigilance; WHO-VigiAccess; Diabetes mellitus

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INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic metabolic disorders worldwide and represents a major and growing public health challenge. According to the International Diabetes Federation (IDF), the global burden of diabetes is expected to increase substantially, with the number of adults living with diabetes projected to reach approximately 853 million by 2050¹. The increasing prevalence of diabetes has resulted in extensive use of pharmacological therapies to achieve adequate glycaemic control and reduce the risk of long-term complications. Commonly used antidiabetic drug classes include biguanides, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists².

Although antidiabetic medications provide substantial clinical benefits, their use may be associated with a wide range of adverse drug reactions (ADRs), ranging from mild gastrointestinal disturbances and hypoglycaemia to serious and potentially life-threatening events³. The safety information obtained from pre-marketing clinical trials is valuable; however, clinical trials are often limited by relatively small sample sizes, strict eligibility criteria, selected patient populations, and limited follow-up durations. Consequently, some uncommon, delayed, or population-specific adverse events may only become evident after a medicine is widely used in routine clinical practice⁴. Pharmacovigilance is therefore an essential component of medicine safety surveillance, particularly during the post-marketing period. Spontaneous adverse event reporting systems enable the detection and assessment of suspected safety signals in large and diverse

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populations. The WHO programme for International drug monitoring collects reports of suspected adverse drug reactions from participating countries, and VigiAccess provides public access to aggregated information from the global individual case safety report database. Thus, VigiAccess represents a valuable resource for exploring patterns of adverse event reporting at the global level 5-7 Previous studies have evaluated the safety profiles of individual antidiabetic medicines and specific drug classes; however, comparative analyses describing the global distribution of reported adverse events across major antidiabetic drug classes remain relatively limited 2,3,8. In particular, examining the distribution of reports according to age, sex, geographical region, and MedDRA System Organ Class (SOC) may provide a broader understanding of the post-marketing safety profiles of these medicines.

Therefore, the present study aims to describe the global patterns of adverse event reporting associated with major classes of antidiabetic drugs using data obtained from the WHO-VigiAccess database. The study focuses on the frequency and distribution of reported adverse events according to demographic characteristics, geographical distribution, and MedDRA System Organ Classes. Such an analysis may contribute to a better understanding of reported safety patterns and support continued pharmacovigilance of widely used antidiabetic therapies.

MATERIAL AND METHODS

Study design: A cross-sectional, descriptive pharmacovigilance study was conducted to evaluate global ADR reporting patterns associated with major antidiabetic drug classes using data obtained from the WHO-VigiAccess database.

Data source and study period: Data were obtained from WHO-VigiAccess, the publicly accessible interface of the WHO programme for International drug monitoring global individual case safety report database. VigiAccess provides aggregated information on suspected ADR reports submitted through the global pharmacovigilance system, including information on patient demographics, geographical distribution, and reported adverse reactions. The date of data retrieval was recorded for each drug because the VigiAccess database is continuously updated. **Drugs included in the study:** The analysis included selected antidiabetic drugs from five major pharmacological classes:

- Biguanide: Metformin
- Sulfonylureas: Glimepiride, Gliclazide, and Glibenclamide
- DPP-4 inhibitors: Sitagliptin, Vildagliptin, Linagliptin, and Saxagliptin
- SGLT2 inhibitors: Dapagliflozin, Empagliflozin, and Canagliflozin
- GLP-1 receptor agonists: Semaglutide, Liraglutide, and Dulaglutide

Data collection: Each selected drug was searched individually in the WHO-VigiAccess database. The aggregated ADR information available for each drug was systematically extracted and recorded in a standardized microsoft excel spreadsheet. The following variables were collected for each drug: Total number of reported ADR

cases, Age distribution of reported cases, Sex distribution, Geographical distribution, frequently reported MedDRA System Organ Classes. The extracted information was cross-checked with the corresponding VigiAccess database display to ensure accuracy and consistency.

Inclusion Criteria: The study included selected antidiabetic drugs belonging to the predefined pharmacological classes that were available as individual drug entries in the WHO-VigiAccess database. Only drugs for which publicly accessible aggregated ADR information was available were included. Drug entries containing sufficient information for the planned descriptive analysis, including demographic characteristics, geographical distribution, and reported adverse events, were considered eligible for inclusion.

Exclusion Criteria: Fixed-dose combination products and combination antidiabetic preparations were excluded from the analysis to ensure that the assessment was restricted to individual antidiabetic drugs.

Study Outcomes: The primary outcome was the frequency and distribution of reported adverse events associated with the selected antidiabetic drugs and their respective pharmacological classes. Secondary outcomes included the distribution of ADR reports according to age and sex, geographical reporting patterns, and identification of the most frequently reported MedDRA SOCs. The study also described differences in ADR reporting patterns among the five selected antidiabetic drug classes.

Statistical Analysis: Data obtained from WHO VigiAccess were analyzed using descriptive statistics. ADR reports were summarized as frequencies and percentages and compared across individual drugs and pharmacological classes. The distribution of reports was assessed according to geographical region, sex, age group, and SOC. Drugs were ranked according to total ADR reports. Results were presented in tables, bar charts and pie charts.

RESULT

The present WHO-VigiAccess analysis demonstrated substantial variation in global adverse drug reaction reporting patterns across major antidiabetic drug classes. Fig 1 demonstrates substantial variation in the total number of ADR reports among the major antidiabetic drugs included in the WHO VigiAccess analysis. Metformin accounted for the highest number of reported ADRs (203,073), followed by semaglutide (127,132), dulaglutide (86,177), and liraglutide (75,063). Among SGLT2 inhibitors, empagliflozin (58,358) and dapagliflozin (54,998) showed the highest reporting volumes, whereas sitagliptin (37,380) was the most frequently reported DPP-4 inhibitor. Saxagliptin had the lowest number of reports (5,214). (table 1) These findings indicate differences in the volume of spontaneous ADR reporting across drugs; however, reporting counts should not be interpreted as measures of drug-specific risk or incidence because they are strongly influenced by exposure, prescribing volume, duration of market availability, and reporting behaviour.

The drug class-wise distribution of ADR reports is presented in Fig. 2. A total of 759,284 ADR reports were analyzed across the five antidiabetic drug classes. GLP-1

receptor agonists (semaglutide, liraglutide, and dulaglutide) accounted for the highest number of ADR reports (288,372; 37.98%), followed by biguanides (metformin) with 203,073 reports (26.75%). SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) contributed 137,895 reports (18.16%), while DPP-4 inhibitors (sitagliptin, vildagliptin, linagliptin, and saxagliptin) accounted for 77,625 reports (10.22%). The lowest number of ADR reports was observed with sulfonylureas (glimepiride, gliclazide, and glibenclamide), with 52,319 reports (6.89%). Overall, the distribution demonstrated considerable variation in the number of reported ADRs among the different antidiabetic drug classes, with GLP-1 receptor agonists representing the largest proportion of reports and sulfonylureas the smallest.

Marked regional variations were observed in the reporting of ADRs among the different antidiabetic drug classes. (Fig. 3) America showed the highest contribution to ADR reporting for most of the drugs, particularly for canagliflozin, dulaglutide, liraglutide, semaglutide, saxagliptin, and empagliflozin. The highest regional value was observed for canagliflozin (86%), followed by dulaglutide (81%) and liraglutide (68%). Asia demonstrated comparatively higher ADR reporting for several sulfonylureas and DPP-4 inhibitors. The highest Asian contribution was observed for vildagliptin (70%), followed by linagliptin (65%), gliclazide (62%), and glimepiride (59%). For metformin, ADR reports were predominantly from America (45%), followed by Asia (35%) and Europe (17%). Among the SGLT2 inhibitors, America accounted for the largest proportion of reports, particularly for canagliflozin, while Europe contributed substantially to reports for dapagliflozin and empagliflozin. Similarly, among the GLP-1 receptor agonists, America was the predominant reporting region for semaglutide, liraglutide, and dulaglutide, with Europe contributing the next largest proportion. Africa and Oceania contributed relatively fewer ADR reports across all the drugs evaluated.

ADR reports showed a predominance among males for Metformin, Gliclazide, Semaglutide, Liraglutide, and Dulaglutide, whereas females accounted for a higher proportion of reports associated with Vildagliptin,

Linagliptin, Dapagliflozin, and Empagliflozin. Glimepiride demonstrated an almost equal distribution of ADR reports between males and females. Among the GLP-1 receptor agonists, a marked male predominance was observed with Liraglutide (71%) and Semaglutide (64%). Reports with unknown sex constituted a relatively small proportion across all the evaluated drugs. The findings demonstrated a slight male predominance in spontaneous ADR reporting, although the sex distribution varied across individual antidiabetic agents. (Fig 4)

The age-wise distribution of ADR reports showed that 45–64 years was the most frequently represented age group across most antidiabetic medications. A considerable proportion of reports was also unknown age, particularly for dulaglutide, semaglutide, and dapagliflozin. Reports among children and adolescents were comparatively low. ADR reporting was predominantly observed among middle-aged and older adults, with relatively fewer reports in younger age groups. (Fig 5)

The distribution of reported potential side effects across the evaluated antidiabetic medications demonstrated considerable variation between drug classes and SOC. Gastrointestinal disorders were the most prominently reported adverse-effect category overall, with particularly high reporting for metformin, vildagliptin, linagliptin, canagliflozin, glimepiride and dulaglutide also showed notable reporting in this category. Among the drug-specific patterns, metformin showed a marked predominance of gastrointestinal adverse effects, whereas vildagliptin, linagliptin, and canagliflozin exhibited comparatively high reporting across gastrointestinal and other systemic categories. The incretin-based therapies, including semaglutide, liraglutide, and dulaglutide, showed notable reporting of gastrointestinal and metabolic/nutritional events. SGLT2 inhibitors, particularly dapagliflozin and empagliflozin, demonstrated relatively higher reporting in renal/urinary and metabolic categories compared with several other medications. In contrast, categories such as blood and lymphatic disorders, cardiac disorders, endocrine disorders, eye disorders, psychiatric disorders, and vascular disorders generally had lower numbers of reported events across most medications.

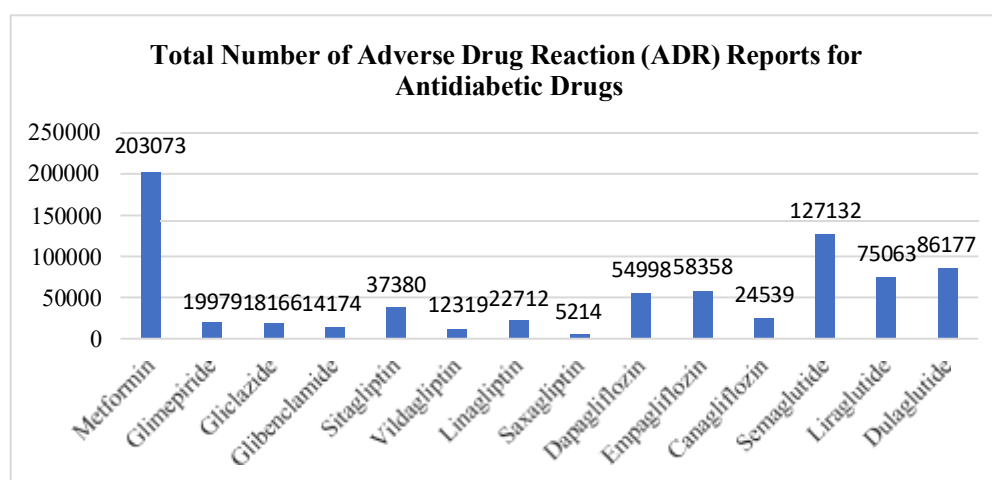
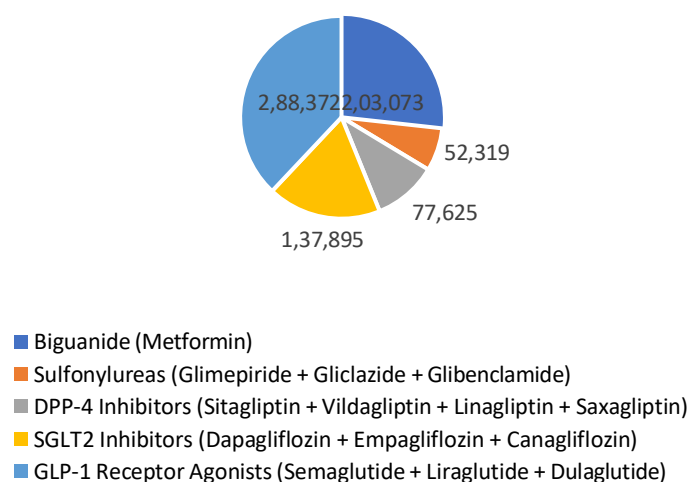
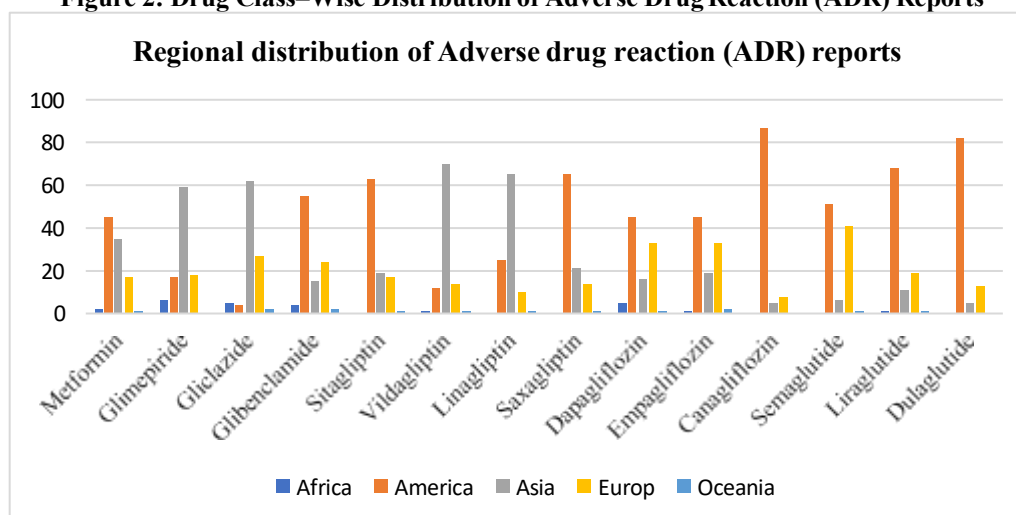


Figure 1: Total Number of Adverse Drug Reaction (ADR) Reports for Antidiabetic Drugs

Table 1: Ranking of Antidiabetic Drugs According to ADR Reporting Frequency

Rank Order	Class	ADR Reporting
1	Metformin	203,073
2	Semaglutide	127,132
3	Dulaglutide	86,177
4	Liraglutide	75,063
5	Empagliflozin	58,358
6	Dapagliflozin	54,998
7	Sitagliptin	37,380
8	Canagliflozin	24,539
9	Linagliptin	22,712
10	Glimepiride	19,979
11	Gliclazide	18,166
12	Glibenclamide	14,174
13	Vildagliptin	12,319
14	Saxagliptin	5,214

Drug Class–Wise Distribution of Adverse Drug Reaction (ADR) Reports**Figure 2: Drug Class–Wise Distribution of Adverse Drug Reaction (ADR) Reports****Figure 3: Regional distribution of Adverse Drug Reaction (ADR) Reports**

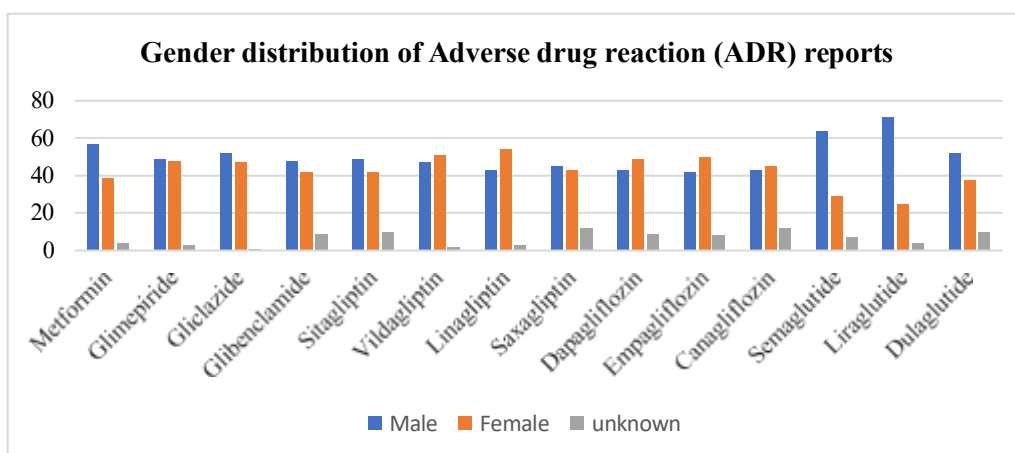


Figure 4: Gender distribution of Adverse Drug Reaction (ADR) Reports

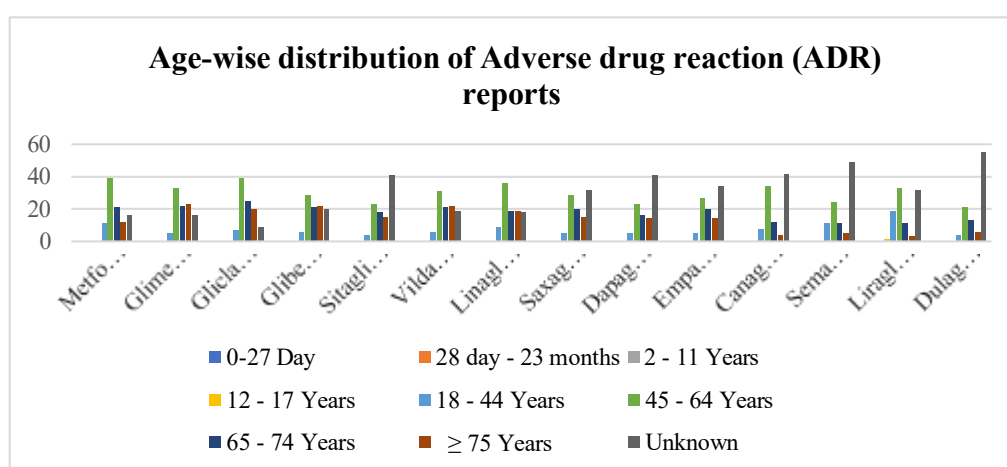


Figure 5: Age-wise distribution of Adverse Drug Reaction (ADR) Reports

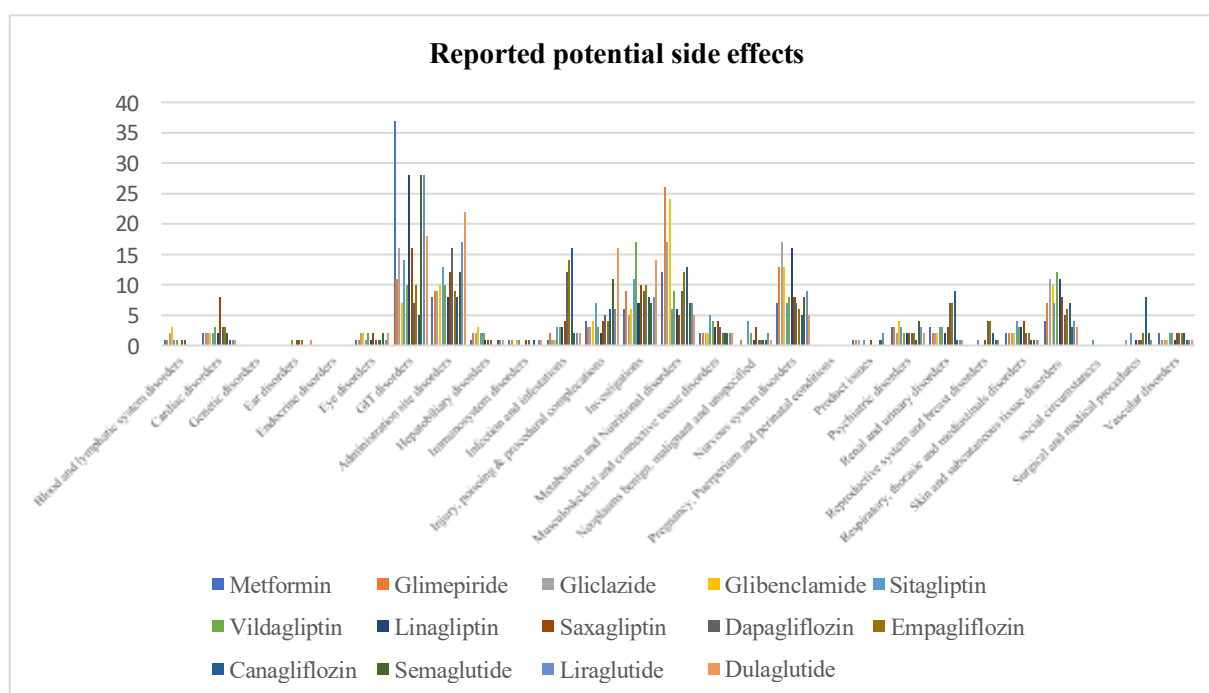


Figure 6: Reported potential side effects across major antidiabetic drugs.

DISCUSSION

The present WHO-VigiAccess analysis demonstrated substantial variation in global adverse drug reaction reporting patterns across major antidiabetic drugs. Metformin had the highest number of reports among individual drugs, while GLP-1 receptor agonists accounted for the greatest overall reporting among the studied drug classes. The distribution of reports varied considerably according to geographical region, age, and sex, with most reports originating from middle-aged and older adults and from America, Asia, and Europe.

Metformin accounted for the highest number of ADR reports (203,073) among the drugs evaluated. This finding is likely attributable to the widespread use of metformin as a first-line pharmacological treatment for type 2 diabetes mellitus (T2DM) and its long-standing availability worldwide. Importantly, a higher number of spontaneous ADR reports does not necessarily indicate a poorer safety profile. The reporting frequency may be influenced by several factors, including drug utilization, duration of market exposure, prescribing frequency, patient population, and reporting practices. Thus, the high number of reports associated with metformin may primarily reflect its extensive clinical utilization rather than an intrinsically higher risk of adverse effects. Similar observations have been reported by Bailey CJ et al. and Beninger P, who emphasized the frequent reporting of metformin in spontaneous pharmacovigilance databases, reflecting its well-established role and widespread use in diabetes management^{9,4}.

Among the newer antidiabetic agents included in the present analysis, semaglutide accounted for the highest number of ADR reports. This finding may be related to the rapid expansion of semaglutide use in clinical practice, increasing exposure of patients to the drug and consequently increasing the opportunity for ADR reporting. In addition, heightened clinical awareness and increased pharmacovigilance attention toward newer agents may contribute to greater reporting. Recent pharmacovigilance studies have similarly demonstrated a marked increase in adverse event reports associated with GLP-1 receptor agonists, particularly semaglutide and liraglutide, corresponding with their increasing clinical utilization¹⁰. One global analysis of GLP-1 receptor agonists reported more than 250,000 adverse event reports in the FAERS database, further supporting the increasing volume of safety reports associated with this therapeutic class¹¹. In contrast, saxagliptin demonstrated the lowest number of ADR reports among the antidiabetic drugs evaluated in the present study. This observation is consistent with findings reported by Scheen AJ, who noted that saxagliptin generated fewer spontaneous safety reports than more frequently prescribed DPP-4 inhibitors such as sitagliptin and linagliptin¹². However, the lower reporting frequency should not be interpreted as definitive evidence of superior safety, as spontaneous reporting systems are influenced by prescribing volume, duration of exposure, reporting behavior, and other confounding factors. At the therapeutic class level, GLP-1 receptor agonists accounted for the

highest proportion of ADR reports, followed by biguanides and SGLT2 inhibitors. The prominent contribution of GLP-1 receptor agonists may reflect their rapidly increasing clinical use, particularly the widespread adoption of semaglutide and liraglutide¹⁰. Furthermore, the introduction and increasing utilization of newer antidiabetic agents have resulted in greater pharmacovigilance activity and increased recognition and reporting of their adverse events. The ADR reporting data should be interpreted cautiously because reporting frequency alone cannot be used to estimate the incidence or comparative risk of ADRs. Further studies incorporating drug utilization data, exposure-adjusted reporting rates, and clinical characteristics of reported cases would be useful to better assess the safety profiles of individual antidiabetic agents. The present study demonstrated considerable geographical variation in ADR reporting among antidiabetic drugs. America contributed the highest proportion of reports for several agents, including canagliflozin, dulaglutide, liraglutide, saxagliptin, and sitagliptin. This predominance may be related to extensive antidiabetic drug utilization, established pharmacovigilance infrastructure, and greater awareness and participation in spontaneous ADR reporting in North America^{4,13}. Asia was the major reporting region for vildagliptin, linagliptin, gliclazide, and glimepiride, which may reflect the substantial burden of diabetes and widespread use of these agents across Asian countries¹⁴. Europe contributed considerably to reports associated with semaglutide, dapagliflozin, and empagliflozin, consistent with the well-established European pharmacovigilance system and reporting through EudraVigilance¹⁵.

The substantial contribution of America and Asia to metformin-related ADR reports is likely to reflect its widespread and long-standing use in diabetes management rather than a higher inherent risk of ADRs.⁹ Conversely, the relatively low contribution from Africa and Oceania may be influenced by differences in healthcare access, drug utilization, awareness of ADR reporting, and the availability and strength of pharmacovigilance systems. Similar limitations in ADR reporting from African settings have been reported previously¹⁶. The observed geographical differences are likely to reflect a combination of drug utilization, prescribing patterns, healthcare infrastructure, pharmacovigilance capacity, and reporting behavior. Since WHO-VigiAccess data are based on spontaneous reports, these regional variations cannot be directly interpreted as differences in ADR incidence or comparative drug safety.

Male predominance was observed for metformin, gliclazide, and the GLP-1 receptor agonists semaglutide, liraglutide, and dulaglutide, with particularly higher male reporting for liraglutide (71%) and semaglutide (64%). In contrast, female predominance was observed for vildagliptin, linagliptin, dapagliflozin, and empagliflozin, while glimepiride showed an approximately balanced distribution between males and females. These findings may be influenced by differences in drug utilization, disease burden, pharmacokinetic characteristics, and healthcare-seeking behaviour between men and women. Previous

research by Zucker et al. and Regitz-Zagrosek has highlighted that biological sex and gender-related factors can influence drug exposure, treatment patterns, and spontaneous ADR reporting 17,18. The relatively high number of reports associated with semaglutide and liraglutide may also reflect their increasing global use, rather than indicating a higher ADR risk among males. Furthermore, sex-related differences in body composition, gastrointestinal physiology, hormonal regulation, and pharmacokinetics may contribute to variations in adverse-event profiles associated with GLP-1 receptor agonists 19. The female predominance observed with dapagliflozin and empagliflozin is consistent with reports suggesting higher ADR reporting among women, particularly for genitourinary infections associated with SGLT2 inhibitors 20,21. Women may also have greater healthcare utilization and may be more likely to report adverse events, which can contribute to differences in spontaneous reporting between sexes 22.

Age-wise, most ADR reports were observed among patients aged 45–64 years, particularly for metformin, gliclazide, linagliptin, canagliflozin, and liraglutide 23,24. Reports among patients aged 65–74 years accounted for approximately 11–25% for several medications, while patients aged ≥ 75 years contributed notably to reports involving sulfonylureas, particularly glimepiride and glibenclamide, as well as vildagliptin. This distribution is consistent with the increasing prevalence of diabetes and greater exposure to antidiabetic therapy after middle age. Older adults are additionally more vulnerable to ADRs because of polypharmacy, multiple comorbidities, and age-related changes in pharmacokinetic and pharmacodynamic responses 25–28. The greater representation of elderly patients in sulfonylurea-related reports may also be associated with their increased susceptibility to hypoglycemia and related complications. In contrast, younger adults accounted for fewer reports, potentially reflecting lower comorbidity burden and greater physiological reserve, while the limited number of pediatric reports corresponds with the comparatively lower prevalence of type 2 diabetes in children 29,30. The results emphasize the significance of middle-aged and older patients in the monitoring of ADRs during antidiabetic medication.

Different ADR patterns among antidiabetic medication classes were shown in this investigation. Gastrointestinal disorders were predominant with metformin, GLP-1 receptor agonists, and selected DPP-4 inhibitors, which is consistent with the established gastrointestinal tolerability profile of these therapies. Metformin commonly causes gastrointestinal symptoms, while GLP-1 receptor agonists may produce nausea, vomiting, and other GI effects through their effects on gastric emptying and gastrointestinal motility 31. Metabolism and nutrition disorders were prominent with sulfonylureas, which is consistent with their glucose-lowering mechanism and established risk of hypoglycemia. Neurological manifestations may also occur secondary to hypoglycemia, particularly with insulin secretagogues 32–34. SGLT2 inhibitors showed a characteristic pattern of infections and renal/urinary

disorders. Increased urinary glucose excretion associated with SGLT2 inhibition may create a favorable environment for genital and urinary infections 35. Renal and urinary ADRs should nevertheless be interpreted in the context of underlying diabetic kidney disease and the renal effects of these agents 36. Dermatological reactions were reported mainly with DPP-4 inhibitors and sulfonylureas. Although uncommon, DPP-4 inhibitors have been associated with cutaneous reactions, including bullous pemphigoid, with evidence suggesting an increased risk compared with sulfonylureas 37,38. Cardiac adverse events were relatively less frequently reported but were more prominent with saxagliptin. This observation is clinically relevant because the SAVOR-TIMI 53 trial demonstrated an increased risk of hospitalization for heart failure with saxagliptin compared with placebo 39. The observed ADR patterns were broadly consistent with the known pharmacological safety profiles of the respective antidiabetic drug classes. Continued pharmacovigilance and comparative clinical studies remain important for identifying emerging safety signals and improving the safe use of antidiabetic therapies. This study highlights important patterns in the safety profile of antidiabetic medications. Metformin and GLP-1 receptor agonists accounted for the highest number of ADR reports, while most reports originated from America, Asia, and Europe. ADRs were predominantly reported among patients aged 45–64 years, with elderly patients showing increased susceptibility to certain sulfonylurea-related events. Gastrointestinal disorders were the most commonly reported ADRs, with class-specific patterns such as hypoglycemia, genitourinary infections, neurological disorders, and dermatological reactions also observed. These findings were consistent with established safety profiles and previous pharmacovigilance evidence, emphasizing the need for continued ADR monitoring and early detection to improve the safe and rational use of antidiabetic medications.

CONCLUSION

The present WHO-VigiAccess analysis demonstrated substantial variation in ADR reporting patterns across major antidiabetic drug classes. Metformin and GLP-1 receptor agonists accounted for the highest reporting volumes, while gastrointestinal disorders were the most frequently reported ADRs. Middle-aged and older adults contributed most reports, with distinct class-specific patterns such as hypoglycemia with sulfonylureas and genitourinary events with SGLT2 inhibitors.

These findings highlight the value of global spontaneous reporting systems such as WHO-VigiAccess for identifying and characterizing patterns of reported adverse events associated with widely used antidiabetic therapies. However, the observed reporting frequencies should not be interpreted as measures of incidence, causality, or comparative drug safety because spontaneous reporting data are influenced by drug utilization, reporting practices, duration of market exposure, and other reporting biases. Continued pharmacovigilance, signal evaluation, and complementary epidemiological studies are therefore important to further characterize the safety profiles of

antidiabetic medications and support their safe and rational use in clinical practice.

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