

Trending Patterns analysis in Metformin-Associated Adverse Events: A Comprehensive Analysis of FAERS Data from 1997 to 2025

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Abstract—Objective: To evaluate the adverse event reporting patterns of metformin using data from the FDA Adverse Event Reporting System (FAERS), with emphasis on signal detection through systematic pattern analysis across demographic variables, geographical distribution, and clinical outcomes.

Methodology: We conducted a comprehensive analysis of metformin-associated adverse event reports from the FAERS database spanning from 1997 to 2025. Reports were categorized and analyzed by System Organ Class (SOC), seriousness criteria, demographic characteristics (age and gender), reporter type, and temporal trends. The search strategy utilized the FAERS Dashboard Open Platform to retrieve all spontaneous reports where metformin was listed as a suspect drug.

Results: A total of 60,835 adverse event reports associated with metformin were identified. Metabolism and Nutrition Disorders constituted the largest proportion of reports (25,483 cases), with lactic acidosis being the most frequently reported specific adverse event (11,613 cases). Elderly patients (≥ 65 years) accounted for 36.67% of reports, while adults aged 18-64 years represented 34.99%. A slightly higher proportion of reports came from females (46.42%) compared to males (40.26%). Healthcare professionals submitted 77.07% of all reports. Notably, 90.6% of reported events were classified as serious, with hospitalization (32.6%) being the most common serious outcome. Reporting frequency showed a marked increase from 2012 onward, peaking in 2020 (11.32% of total reports).

Discussion: The adverse event profile observed largely aligns with metformin's established safety concerns, particularly regarding gastrointestinal effects and the rare but serious risk of lactic acidosis. The predominance of reports from elderly populations highlights the importance of vigilant monitoring in this demographic, particularly given potential age-related decreases in renal function. The increasing temporal trend in reporting likely reflects enhanced pharmacovigilance systems rather than declining drug safety.

Conclusion: This analysis of FAERS data reinforces metformin's known safety profile while providing valuable insights into real-world reporting patterns. Despite limitations inherent to spontaneous reporting systems, these findings support the continued favorable benefit-risk profile of metformin when used with appropriate patient selection and monitoring. Healthcare providers should maintain particular vigilance regarding renal function assessment and signs of lactic acidosis, especially in elderly patients. Future pharmacovigilance efforts should focus on better characterizing risk factors for serious adverse events in vulnerable populations.

Index Terms—

Abbreviation	Full Term
ADR	Adverse Drug Reaction
CSR	Clinical Study Report
DKA	Diabetic Ketoacidosis
DPP-4	Dipeptidyl Peptidase-4
eGFR	estimated Glomerular Filtration Rate
ER/XR	Extended-Release
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
GDM	Gestational Diabetes Mellitus
HbA1c	Hemoglobin A1c
PCOS	Polycystic Ovary Syndrome
PT	Preferred Term
SGLT2	Sodium-Glucose Cotransporter-2
SOC	System Organ Class
T2DM	Type 2 Diabetes Mellitus
UKPDS	United Kingdom Prospective Diabetes Study

I. OBJECTIVE

This adverse event summary report provides a comprehensive overview of the safety profile of Metformin. The data for the report has been sourced

from the FAERS database, focusing on reported adverse events and pattern of adverse event reporting. The report will also highlight the most common adverse events associated with Metformin usage and analyse them SOC wise further characterized by seriousness. The data is also analysed based on geography, gender and age.

Furthermore, systematically summarizing and analysing all identified Adverse Drug Reactions (ADRs), this report will present a clear and concise overview of the safety profile of metformin.

II. DRUG BACKGROUND

Metformin is a cornerstone in the management of type 2 diabetes mellitus, known for its glucose-lowering efficacy and favourable safety profile. Below is a comprehensive, plagiarism-free drug background suitable for inclusion in a review paper.

Metformin, a member of the biguanide class of oral antihyperglycemic agents, has been extensively used for over six decades in the treatment of type 2 diabetes mellitus (T2DM). Originally derived from the plant *Galega officinalis*, its therapeutic potential was recognized in the mid-20th century, leading to its clinical introduction in Europe in the 1950s and later in the United States in 1995.

Metformin primarily acts by reducing hepatic glucose production through inhibition of gluconeogenesis. It also enhances insulin sensitivity in peripheral tissues, particularly skeletal muscle, thereby promoting glucose uptake. Unlike many other antidiabetic agents, metformin does not stimulate insulin secretion, which significantly lowers the risk of hypoglycaemia.

Metformin is administered orally and exhibits an absorption rate of approximately 50–60%. It is not metabolized by the liver and is excreted unchanged via the kidneys. Its half-life ranges between 4 to 8.7 hours, depending on renal function. The drug's onset of action is relatively rapid, and its therapeutic effects are sustained with regular dosing.

While its primary indication remains T2DM, metformin has shown promise in a variety of off-label uses. These include polycystic ovary syndrome (PCOS), obesity, metabolic syndrome, and even cancer prevention and aging-related research. Its role in reducing cardiovascular risk and improving lipid profiles further enhances its clinical utility.

Metformin is generally well-tolerated, with gastrointestinal disturbances such as nausea, diarrhoea, and abdominal discomfort being the most common side effects. A rare but serious adverse effect is lactic acidosis, particularly in patients with renal impairment. Regular monitoring of renal function is therefore recommended during therapy.

Internationally, various brands of metformin are available which includes:

- Glucophage – One of the earliest and most widely recognized brands.
- Glucophage XR – Extended-release formulation for improved tolerability.
- Glumetza – Extended-release metformin with a unique delivery system.
- Fortamet – Another extended-release version.
- Riomet – Liquid formulation, often used for pediatric or dysphagic patients.
- Invokamet / Invokamet XR – Combination of canagliflozin and metformin.
- Kazano – Combination of alogliptin and metformin.

There are other brands which are available in India which includes Glycomet (USV), Metlong (Macleods), Obimet (Abbott), Gluformin (Sun Pharma), Zomet (FDC), Cetapin (Sanofi), Diapride-M (Micro Labs), Glyciphage (Franco-Indian), Metride (Aristo) and Voglibite-M (Mankind) etc.

2.1 Indication

Metformin is primarily approved for the treatment of type 2 diabetes mellitus, but it also has several other recognized medical uses:

FDA approved indication includes:

- Type 2 Diabetes Mellitus (T2DM): Metformin is indicated as a first-line therapy to improve glycemic control in adults and children aged 10 years and older with T2DM. It can be used as monotherapy or in combination with other antidiabetic agents such as sulfonylureas, insulin, or newer classes like SGLT2 inhibitors and DPP-4 inhibitors.
- Prevention of Type 2 Diabetes (Off-label but supported): Although not formally approved for diabetes prevention, metformin is often used in individuals with prediabetes, especially those who are overweight or have a history of gestational diabetes. The Diabetes Prevention Program (DPP)

trial demonstrated its efficacy in delaying the onset of T2DM.

- Polycystic Ovary Syndrome (PCOS): Metformin is frequently prescribed off-label for PCOS to improve insulin resistance, regulate menstrual cycles, and support ovulation. While not FDA-approved for this indication, its use is supported by clinical guidelines and widespread practice.
- Gestational Diabetes Mellitus (GDM): Metformin is sometimes used off-label in pregnant women with GDM when lifestyle modifications are insufficient and insulin therapy is not preferred. Its safety profile in pregnancy is still under evaluation, but it is increasingly considered a viable alternative to insulin.

2.2 Qualitative and Quantitative Composition

Metformin is available in several approved formulations, including immediate-release tablets, extended-release tablets, oral solutions, and fixed-dose combinations with other antidiabetic agents.

Immediate-Release Tablets

- Strengths: Commonly available in 250 mg, 500 mg, 850 mg, and 1000 mg.
- Usage: Typically taken 2–3 times daily with meals to reduce gastrointestinal side effects.
- Brands: Glucophage, Glycomet, Cetapin, Obimet.

Extended-Release (ER/XR) Tablets

- Strengths: Usually available in 500 mg, 750 mg, and 1000 mg.
- Usage: Taken once daily, often at night, to improve tolerability and adherence.
- Brands: Glucophage XR, Fortamet, Glumetza, Glycomet XR.

Oral Solution/Syrup

- Strengths: Typically 500 mg/5 mL.
- Usage: Ideal for pediatric patients or those with difficulty swallowing tablets.
- Brands: Riomet (U.S.), Metformin Oral Solution (India).

Fixed-Dose Combinations (FDCs)

Metformin is combined with other antidiabetic agents to enhance glycemic control:

- With Sulfonylureas:
 - Glipizide + Metformin (e.g., Metaglip)
 - Glyburide + Metformin (e.g., Glucovance)
- With DPP-4 Inhibitors:
 - Sitagliptin + Metformin (e.g., Janumet)

- Vildagliptin + Metformin (e.g., Galvus Met)
- With SGLT2 Inhibitors:
 - Canagliflozin + Metformin (e.g., Invokamet)
 - Empagliflozin + Metformin (e.g., Synjardy)
- With Thiazolidinediones:
 - Pioglitazone + Metformin (e.g., Actoplus Met)
- With Alpha-glucosidase inhibitors:
 - Voglibose + Metformin (e.g., Voglibite-M)

2.3 Safety profile

Metformin has a long-standing reputation for safety in the management of type 2 diabetes mellitus. Its mechanism of action—primarily reducing hepatic glucose production and improving insulin sensitivity—does not involve stimulating insulin secretion, which significantly lowers the risk of hypoglycemia. This makes it a preferred first-line agent for most patients.

2.3.1 Adverse Drug Reactions

Metformin is generally considered safe and well-tolerated, with gastrointestinal disturbances being the most common adverse events. Rare but serious risks include lactic acidosis, especially in patients with renal impairment

Key safety advantages include:

- Low risk of hypoglycemia when used alone.
- Weight neutrality or modest weight loss, beneficial for overweight patients.
- Cardiovascular protection, as shown in long-term studies like the UKPDS.

However, its use requires caution in certain populations, particularly those with impaired renal function, hepatic disease, or conditions predisposing to hypoxia.

Common Adverse Events

The most frequently reported side effects are gastrointestinal in nature, especially during the initial weeks of therapy:

- Nausea
- Diarrhea
- Abdominal discomfort
- Flatulence
- Metallic taste

These symptoms are dose-dependent and often improve with gradual dose titration or switching to extended-release formulations.

Serious Adverse Events

1. Lactic Acidosis

- A rare but potentially fatal complication.

- Occurs in
- Risk increases in patients with renal impairment, heart failure, liver disease, or alcohol abuse.
- Symptoms include malaise, myalgia, respiratory distress, and altered mental status.

2. Vitamin B12 Deficiency

- Long-term use may impair B12 absorption.
- Can lead to anemia and neuropathy.
- Monitoring is recommended in patients on prolonged therapy.

3. Hepatic and Renal Concerns

- Not recommended in patients with eGFR
- Liver dysfunction may increase the risk of lactic acidosis.

2.3.2 Adverse Event Reporting

A descriptive analysis using Vigibase data revealed that gastrointestinal disorders accounted for over 60% of reported adverse events. Other notable categories included metabolic disturbances, skin reactions, and nervous system effects.

Clinical Considerations

- Start low, go slow: Initiating therapy at low doses and gradually increasing helps minimize GI side effects.
- Monitor renal function: Regular assessment of eGFR is essential.
- Assess B12 levels: Especially in elderly or long-term users.

2.3.2 Monitoring

Metformin is a widely used oral antidiabetic medication primarily for type 2 diabetes management. The following monitoring precautions should be taken when administering metformin:

Before Initiating Therapy

- Renal Function Assessment: Check baseline kidney function (eGFR/creatinine clearance) as metformin is contraindicated in patients with significantly impaired renal function
- Liver Function Tests: Assess hepatic function as severe liver disease may increase risk of lactic acidosis
- Vitamin B12 Levels: Consider baseline measurement as long-term metformin use can decrease vitamin B12 absorption

During Therapy

Regular Monitoring

- Renal Function:

- Blood Glucose Levels: Regular monitoring to assess therapeutic effectiveness
- HbA1c Levels: Check every 3-6 months to evaluate long-term glycemic control
- Vitamin B12 Levels: Periodic monitoring, especially in patients on long-term therapy or with anemia/peripheral neuropathy symptoms
- Signs of Lactic Acidosis

Special Monitoring Situations

- Before and After Radiologic Studies with Iodinated Contrast: Temporarily discontinue metformin before or at the time of the procedure; restart only after renal function reassessment
- Before Surgery: May need to temporarily discontinue before surgical procedures involving restricted intake of food and fluids
- Elderly Patients: More frequent monitoring of renal function
- Patients with Heart Failure, Liver Disease, or Alcohol Abuse: Closer monitoring due to increased risk of lactic acidosis

Other Considerations

- Monitor for gastrointestinal side effects (common with initiation)
- Consider drug interactions with medications that may affect renal function or increase risk of lactic acidosis
- Patient education on signs requiring immediate medical attention

2.3.4 Contraindications

Metformin is contraindicated in several conditions due to safety concerns, particularly the increased risk of lactic acidosis in certain patient populations. Here are the key contraindications:

Absolute Contraindications

Renal Impairment

- Severe renal dysfunction: eGFR <30 mL/min/1.73m²

Some guidelines may use different thresholds (e.g., serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females)

Metabolic Conditions

Diabetic ketoacidosis (DKA) or diabetic coma

- Acute or chronic metabolic acidosis, including lactic acidosis, with or without coma
- Hypersensitivity: Known hypersensitivity to metformin or any components of the formulation

- Severe Acute Conditions
- Acute heart failure or cardiogenic shock
- Acute myocardial infarction
- Severe sepsis or shock
- Severe respiratory failure

Hepatic Impairment

- Severe liver disease or clinical/laboratory evidence of hepatic disease

Temporary Contraindications

- Iodinated contrast procedures: Metformin should be discontinued at or prior to the procedure and not restarted until renal function has been re-evaluated and found to be normal
- Major surgical procedures: Temporarily discontinue during the procedure and until oral intake has resumed and renal function is normal

Acute Illness

- Acute serious illness that may affect renal function (severe infection, trauma, etc.)

- Dehydration or severe vomiting/diarrhea

Relative Contraindications (Use with Caution)

- Moderate renal impairment (eGFR 30-45 mL/min/1.73m²): Requires dose adjustment and careful monitoring
- Age >80 years without adequate renal function assessment
- Alcohol abuse or binge drinking

- Heart failure, especially if unstable or acute
- Chronic respiratory disease with hypoxemia
- Advanced age with reduced muscle mass and renal function
- Concurrent medications that may impair renal function or increase risk of lactic acidosis

Pregnancy and Breastfeeding

Generally, not contraindicated but requires individual risk-benefit assessment. In some cases, insulin may be preferred during pregnancy

III. DATA COLLECTION AND STRATEGY

3.1 Data Source

Data for this report was retrieved from the FAERS database. The FAERS (FDA Adverse Event Reporting System) database is a repository of adverse event reports submitted to the U.S. Food and Drug Administration (FDA). It contains information on adverse events, medication errors, and product quality issues associated with various FDA-regulated products such as drugs, biologics, medical devices, dietary supplements, and cosmetics.

A detailed strategy used for retrieval of the data is summarized below in Table 1

Table 1 Search criteria used for data retrieval

Criteria	Search Criteria used in this report
Reporting period	Cumulative through the provided extract
Database search cut-off date	30 September 2025
Report sources	Spontaneous
Suspect drug(s)	Metformin (all product names)
Search engine	FAERS Dashboard Open Platform
Notes on search	All adverse events reported in the extract

IV. METHODOLOGY OF ANALYSIS OF DATA

To review the safety profile of metformin, the reported adverse events were thoroughly reviewed and documented. This analysis aimed to identify patterns, trends, and potential safety concerns associated with the medication. The data available in various tabs was meticulously reviewed and analyzed in the following categories.

SOCs

A comprehensive assessment was conducted to determine the distribution of adverse events across different system organ classes (SOCs). The seriousness of these events was also evaluated and presented. A detailed SOC-wise analysis was performed to identify any specific safety findings that contributed significantly to the total number of reported cases.

Geographical Distribution

A geographical analysis was conducted to understand the distribution of adverse events in different regions. By examining this data, potential variations or trends in the occurrence of adverse events across geographic locations were identified.

Gender

The data was further examined to assess if there were any gender-related differences in the reporting of adverse events. This analysis provided insights into potential variations in the occurrence and severity of adverse events between male and female patients.

Age

To better understand the impact of age on adverse event occurrence, the data was categorized and analyzed according to different age groups. This allowed determination of whether any age-specific

patterns or trends existed in the reporting of adverse events.

Reporter Type

The data was further examined to assess if there were any differences in reporting of adverse events by reporter type. This analysis provided valuable insights into potential variations in reports submitted by healthcare professionals (medically confirmed) versus consumers/non-healthcare professionals (non-medically confirmed).

V. RESULTS

Data Overview

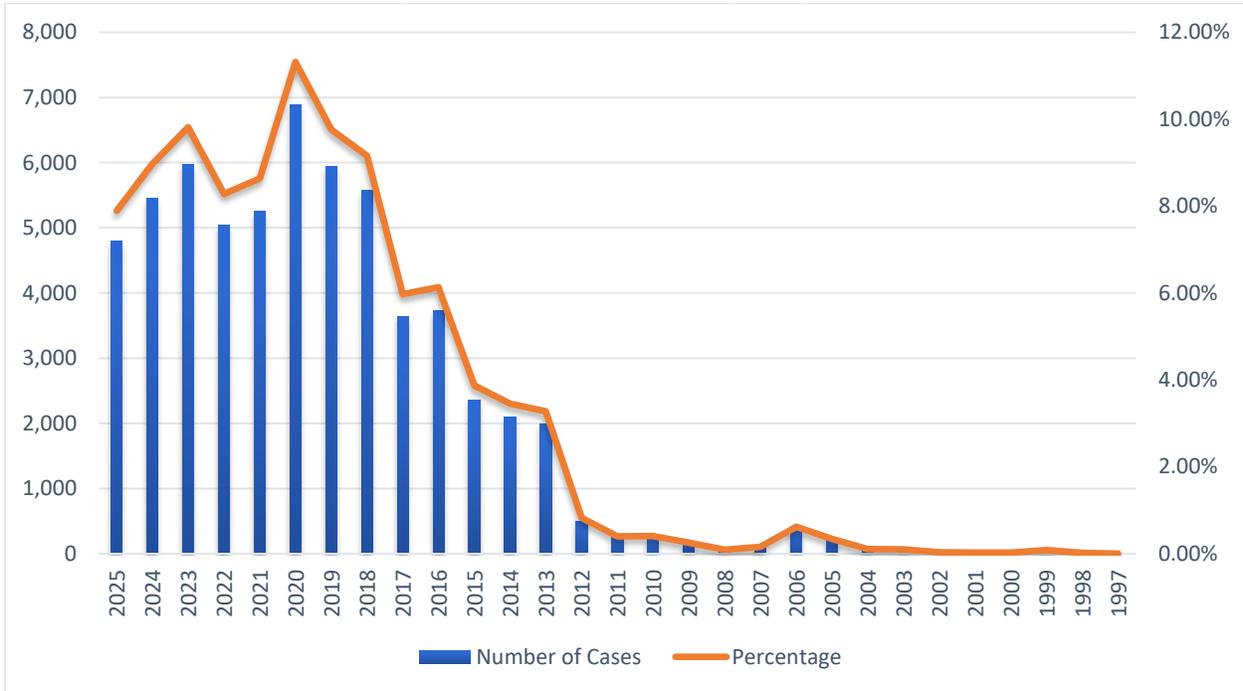
A total of 60,835 case reports (expedited and non-expedited) were retrieved with Metformin from the FAERS database up to 2025. The details of these cases are categorized based on SOC, age, gender, and geography. Refer to below Table 2 for details

Table 2 Distribution of Cases by received year

Time period	Number of Cases	Percentage
2025	4,802	7.89%
2024	5,457	8.97%
2023	5,973	9.82%
2022	5,037	8.28%
2021	5,252	8.63%
2020	6,884	11.32%
2019	5,936	9.76%
2018	5,570	9.16%
2017	3,633	5.97%
2016	3,730	6.13%
2015	2,354	3.87%
2014	2,100	3.45%
2013	1,993	3.28%
2012	500	0.82%
2011	244	0.40%
2010	248	0.41%
2009	153	0.25%
2008	54	0.09%
2007	94	0.15%
2006	378	0.62%
2005	207	0.34%
2004	63	0.10%
2003	60	0.10%

2002	19	0.03%
2001	17	0.03%
2000	14	0.02%
1999	51	0.08%
1998	10	0.02%
1997	2	0.00%
Total	60,835	100.00%

Figure 1 Counts of Cases over Reporting Years



(A horizontal bar chart depicting the number of cases received per year. The distribution peaked in 2020, accounting for 11.32% of total cases.)

- The count includes various reports including expedited, non-expedited, and direct.
- Direct reports are voluntarily submitted to EudraVigilance by consumers and healthcare professionals.
- Mandatory reports are submitted by the manufacturer and are categorized as:

Expedited reports – contain at least one adverse event not described in the product labelling and for which the outcome is serious.

Non-expedited reports – do not meet expedited criteria, may include serious/expected or non-serious cases.

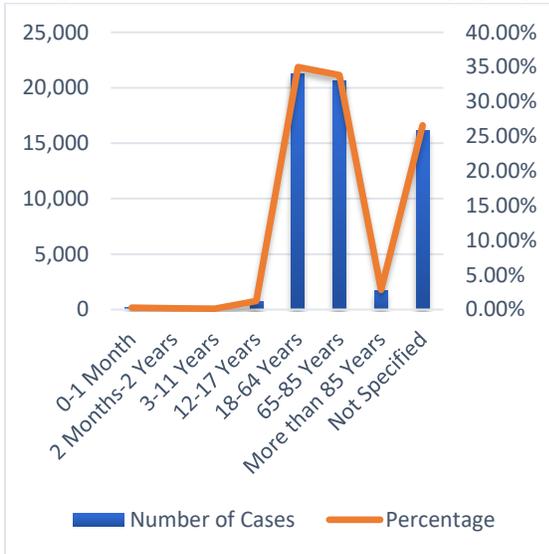
5.1 DISTRIBUTION OF OVERALL CASES BY AGE GROUP

Of the total 60,835 cases where the age group was reported, most of the cases are from the elderly age group (n=22,307; 36.67%), followed by the adult group (n=21,284, 34.99%). The remaining age groups each account for less than 2% of the total. Additionally, there were 16,155 cases (26.56%) where no information regarding the age group was reported. The details are presented in Table 2 and below. Please note: The elderly group includes patients ≥65 years of age.

Table 3 Distribution pattern of Metformin cases by age grouping

Category	Number of Cases	Percentage
0-1 Month	156	0.26%
2 Months-2 Years	109	0.18%
3-11 Years	73	0.12%
12-17 Years	749	1.23%
18-64 Years	21,284	34.99%
65-85 Years	20,589	33.84%
More than 85 Years	1,720	2.83%
Not Specified	16,155	26.56%
Total	60,835	100.00%

Figure 2 Distribution of cases across age groups



5.2 DISTRIBUTION OF CASES BY GENDER

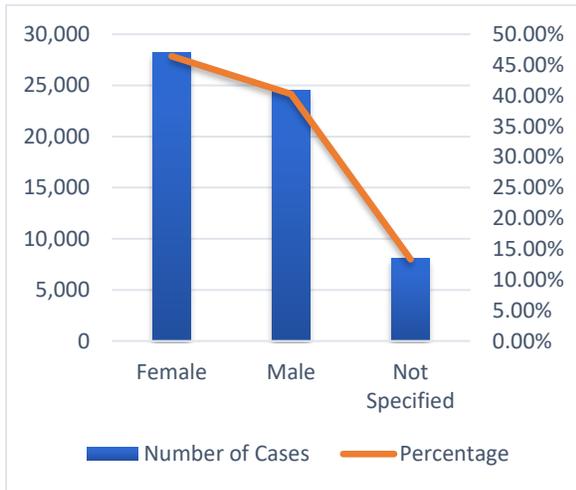
Of the total 60,835 cases, 28,240 (46.42%) were reported in females, 24,493 cases (40.26%) were reported in males, and for the remaining 8,102 cases (13.32%), no information regarding gender was reported. The details are presented in

Table 4 and Figure 3 below.

Table 4 Distribution of cases via Gender

Category	Number of Cases	Percentage
Female	28,240	46.42%
Male	24,493	40.26%
Not Specified	8,102	13.32%
Total	60.835	100.00%

Figure 3 Pattern of distribution pattern of cases by Gender/Sex with percentages



From the Figure 3 it is clearly evident that majority of the cases are reported in female population which accounts for 46.42% of the total cases reported. However, no specific trend is seen in adverse event reporting based on gender.

5.3 DISTRIBUTION OF CASES BY REPORTER TYPE

For metformin, the adverse event cases were primarily reported by Healthcare Professionals (n=46,884), followed by Consumers (n = 12,679). A very small proportion of cases were reported under the category Not Specified reports accounted for 1,272 cases. This indicates that slightly more than half of the cases originated from healthcare professionals, with consumers contributing to nearly half of the reports. The pattern is presented in Table 5

Table 5 The details of the distribution by reporter type

Reporter type	Number of Cases	Percentage
Healthcare Professional	46,884	77.07%
Consumer	12,679	20.84%
Not Specified	1,272	2.09%
Total	9,657	100.00%

5.4 DISTRIBUTION OF OVERALL CASES BY OUTCOME

Of the total cases reported from 1997 till 2025 the pattern of event outcome reported is presented in Hospitalizations and Deaths show a sharp rise starting around 2012, peaking in the mid-2010s.

- Life Threatening and Other Outcomes also follow a similar upward trend.

- Non-Serious cases surged notably in 2016, then fluctuated.
- Congenital Anomalies and Disabled outcomes have increased steadily in recent years.
- Required Interventions remain relatively low and stable across the years.

For the detailed analysis of percentage changes in adverse event outcomes (2016–2025), refer to Table 7 for details

Table 7 Representation year-over-year percentage changes in adverse event outcomes (2016–2025)

Year	Congenital Anomaly	Die d	Disabl ed	Hospitali zed	Life Threatening	Non-Serious	Other Outcomes	Required Intervention
2016	-86.67	14.11	-2.13	22.57	74.5	201.88	17.89	-71.43
2017	0	46.05	-15.22	26.07	32.31	-66.38	89.82	75
2018	1975	27.03	153.85	107.23	116.28	20.19	36.64	-28.57

2019	-22.89	18.16	3.03	-7.15	6.32	1.69	16.63	0
2020	-35.94	38.3	19.61	23.94	13.65	-10.3	19.78	-60
2021	-34.15	24.39	-46.72	-26.56	-34.82	-14.7	-13.26	200
2022	103.7	24.34	15.38	5.82	-2.22	5.94	-11.95	16.67
2023	0	25.64	73.33	14.12	41.88	60.19	15.1	0
2024	-16.36	21.98	6.92	-7.42	7.5	-30.11	-6.88	157.14
2025	152.17	5.11	50.36	-7.9	4.23	-26.54	0.29	-27.78

Between 2016 and 2025, the year-over-year percentage changes in adverse event outcomes revealed several notable trends and fluctuations. Congenital anomalies exhibited the most dramatic shifts, with a staggering 1975% increase in 2018 following a sharp 86.67% decline in 2016, resulting in an average annual change of over 200%. Deaths showed moderate variability, peaking with a 46.05% rise in 2017 and dipping by 24.39% in 2021, averaging a 10.37% annual change. Disability cases surged by 153.85% in 2018 but dropped significantly in 2021, reflecting an average change of 25.84%.

Hospitalizations and life-threatening events both saw their highest increases in 2018, with over 100% and 116% growth respectively, while both declined notably in 2021. Their average annual changes were around 15% and 26%. Non-serious outcomes had the highest volatility, with a 201.88% spike in 2016 followed by a 66.38% drop in 2017, averaging 14.19% annually. Other outcomes maintained a steadier trend, peaking in 2017 and averaging a 16.41% change. Lastly, required interventions fluctuated widely, with a 200% increase in 2021 and a 71.43% decrease in 2016, averaging 26.10% annually.

Overall, 2018 stood out as a year of significant increases across most categories, while 2021 marked a period of widespread declines, suggesting potential shifts in reporting, surveillance, or underlying health dynamics during those years. From the figure it is clearly evident that majority of the adverse events reported are serious events (90.6%). From

Table 6, It is clearly evident that 32.6% of the event outcome lead to hospitalization and 36.6% of the events reported other outcomes. The event outcome of life threatening (8.8%) and fatality (10.2%) reported is less than 2% of the total seriousness criteria. There were 9.4% of the total events which were non-serious.

The distribution of all fatal cases (patient died) and life-threatening reported are mentioned in the

Table 6 below. It is important to note that single case analysis for these cases was not possible because of the limitation of the database; therefore, it does not imply that the deaths were caused by metformin. Also, in these fatal cases, the cause of death might be unknown or due to underlying conditions.

The total number of fatal cases reported with metformin is 8,831 (10.2%). The calculations are based on the number of fatal events reported divided by the total events reported with the drug. As the information available takes into account the suspected undesirable effect(s) (adverse reactions) reported in an individual case, and as an individual case may refer to more than one suspected undesirable effect, this does not represent the individual case outcome reported to FAERS, but rather the number of related undesirable effects. Also, maximum deaths were reported in the year 2020 which accounts for 1152 fatal outcomes.

Figure 4 Pattern of event reported with their event outcome

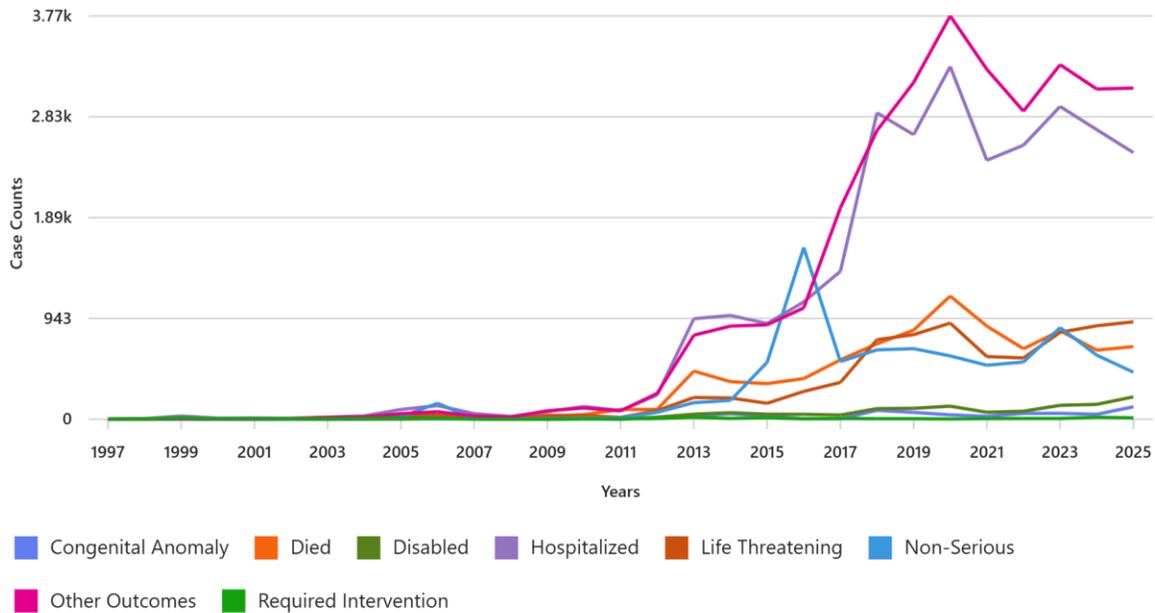


Table 6 Pattern of event seriousness reported till date

Serious Criteria	Event outcome	Percentage
Congenital Anomaly	634	0.7%
Died	8,831	10.2%
Disabled	1,235	1.4%
Hospitalized	28,135	32.6%
Life Threatening	7,630	8.8%
Other Outcomes	31,568	36.6%
Required Intervention	186	0.2%
Non-Serious	8,141	9.4%
TOTAL	86,360	100%

Below mentioned observations were noted

- Hospitalizations and Deaths show a sharp rise starting around 2012, peaking in the mid-2010s.
- Life Threatening and Other Outcomes also follow a similar upward trend.
- Non-Serious cases surged notably in 2016, then fluctuated.

- Congenital Anomalies and Disabled outcomes have increased steadily in recent years.
- Required Interventions remain relatively low and stable across the years.

For the detailed analysis of percentage changes in adverse event outcomes (2016–2025), refer to Table 7 for details

Table 7 Representation year-over-year percentage changes in adverse event outcomes (2016–2025)

Year	Congenital Anomaly	Died	Disabled	Hospitalized	Life Threatening	Non-Serious	Other Outcomes	Required Intervention
2016	-86.67	14.11	-2.13	22.57	74.5	201.88	17.89	-71.43

2017	0	46.05	-15.22	26.07	32.31	-66.38	89.82	75
2018	1975	27.03	153.85	107.23	116.28	20.19	36.64	-28.57
2019	-22.89	18.16	3.03	-7.15	6.32	1.69	16.63	0
2020	-35.94	38.3	19.61	23.94	13.65	-10.3	19.78	-60
2021	-34.15	24.39	-46.72	-26.56	-34.82	-14.7	-13.26	200
2022	103.7	24.34	15.38	5.82	-2.22	5.94	-11.95	16.67
2023	0	25.64	73.33	14.12	41.88	60.19	15.1	0
2024	-16.36	21.98	6.92	-7.42	7.5	-30.11	-6.88	157.14
2025	152.17	5.11	50.36	-7.9	4.23	-26.54	0.29	-27.78

Between 2016 and 2025, the year-over-year percentage changes in adverse event outcomes revealed several notable trends and fluctuations. Congenital anomalies exhibited the most dramatic shifts, with a staggering 1975% increase in 2018 following a sharp 86.67% decline in 2016, resulting in an average annual change of over 200%. Deaths showed moderate variability, peaking with a 46.05% rise in 2017 and dipping by 24.39% in 2021, averaging a 10.37% annual change. Disability cases surged by 153.85% in 2018 but dropped significantly in 2021, reflecting an average change of 25.84%.

Hospitalizations and life-threatening events both saw their highest increases in 2018, with over 100% and 116% growth respectively, while both declined notably in 2021. Their average annual changes were around 15% and 26%. Non-serious outcomes had the highest volatility, with a 201.88% spike in 2016. Table 8 it can be confirmed that more than 40% of the total events are reported from Metabolism and Nutrition Disorders, followed by General Disorders and

followed by a 66.38% drop in 2017, averaging 14.19% annually. Other outcomes maintained a steadier trend, peaking in 2017 and averaging a 16.41% change. Lastly, required interventions fluctuated widely, with a 200% increase in 2021 and a 71.43% decrease in 2016, averaging 26.10% annually.

Overall, 2018 stood out as a year of significant increases across most categories, while 2021 marked a period of widespread declines, suggesting potential shifts in reporting, surveillance, or underlying health dynamics during those years.

VI. THE PATTERN OF DISTRIBUTION OF CASES PER SOCs

From the details presented in

Administration Site Conditions; Injury, Poisoning and Procedural Complications and Gastrointestinal Disorders.

Table 8 Pattern of event reporting by SOC with Reporter Region

SOCs	Domestic	Foreign	Not Specified	Total Cases
Metabolism and Nutrition Disorders	6,060	19,371	52	25,483
General Disorders and Administration Site Conditions	6,513	11,006	76	17,595
Injury, Poisoning and Procedural Complications	5,667	9,878	20	15,565
Gastrointestinal Disorders	5,107	8,788	70	13,965

Renal And Urinary Disorders	2,961	10,572	33	13,566
Investigations	4,985	8,120	129	13,234
Nervous System Disorders	3,030	7,919	34	10,983
Psychiatric Disorders	4,447	4,693	20	9,160
Vascular Disorders	1,933	4,844	10	6,787
Respiratory, Thoracic and Mediastinal Disorders	1,693	4,769	13	6,475
Cardiac Disorders	1,671	4,610	12	6,293
Infections And Infestations	1,408	4,212	19	5,639
Skin And Subcutaneous Tissue Disorders	1,313	3,862	11	5,186
Musculoskeletal And Connective Tissue Disorders	1,389	3,539	21	4,949
Blood And Lymphatic System Disorders	505	2,265	3	2,773
Hepatobiliary Disorders	550	1,854	5	2,409
Eye Disorders	683	1,295	12	1,990
Immune System Disorders	972	735	6	1,713
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	379	1,299	4	1,682
Surgical And Medical Procedures	650	838	20	1,508
Pregnancy, Puerperium and Perinatal Conditions	132	971	5	1,108
Product Issues	520	347	1	868
Congenital, Familial and Genetic Disorders	104	698	1	803
Social Circumstances	218	578	4	800
Endocrine Disorders	122	622	1	745
Ear And Labyrinth Disorders	172	486	1	659
Reproductive System and Breast Disorders	130	506	1	637

In the below section we will be analyzing the pattern of adverse event reporting by SOC and PTs reported in these SOC. Furthermore, the pattern of adverse event reporting will be analyzed against the current safety profile of Sumatriptan and its potential impact on patient safety.

6.1 Metabolism and Nutrition Disorders

In this SOC, most of the cases reported did not specify individual adverse events under the category of Metabolism and Nutrition Disorders. The data indicates a significant number of cases across various age groups and genders. The total fatal events accounted for 7.9 % of the events under this SOC.

Table 9 Pattern of adverse event reporting by PTs (Trend) for Metabolism and Nutrition Disorders

Preferred Term	Number of cases
Lactic Acidosis	11,613
Metabolic Acidosis	3,858
Hypoglycaemia	3,512
Hyperkalaemia	1,791
Dehydration	1,274
Diabetic Ketoacidosis	1,143
Hyperglycaemia	1,121
Decreased Appetite	1,075
Diabetes Mellitus Inadequate Control	1,067

Interpretation of results:

Most cases in this SOC were reported without specification of individual adverse events. The total fatal events accounted for 7.9 % of the events reported under this SOC. Most cases were reported by healthcare professionals. The age and sex distribution indicates that most cases were reported in adults aged 18-64 years, with a higher number of females compared to males.

6.2 General Disorders and Administration Site Conditions

In this SOC, most of the cases reported did not specify individual adverse events under the category of General Disorders and Administration Site Conditions. The data indicates a significant number of cases across various age groups and genders. The total fatal events accounted for 9.5 % of the total events under this SOC.

Table 10 Pattern of adverse event reporting by PTs (Trend) for General Disorders and Administration Site Conditions

Preferred Term	Number of Individual Cases
Drug Ineffective	3,239
Fatigue	2,071
Drug Interaction	1,812
Asthenia	1,662
Malaise	1,628
Condition Aggravated	1,274
Pain	1,247

Interpretation of results:

Most cases in this SOC were reported without specification of individual adverse events. The total fatal events accounted for 9.5 % of the total events reported under this SOC. Most cases were reported by healthcare professionals. The age and sex distribution indicates that most cases were reported in adults aged 18-64 years, with a higher number of females compared to males.

6.3 Injury, Poisoning and Procedural Complications

In this SOC, the majority of the cases reported did not specify individual adverse events under the category of Injury, Poisoning and Procedural Complications. The data indicates a significant number of cases across various age groups and genders. The total fatal events accounted for less than 13.0% of the total events under this SOC.

Table 11 Pattern of adverse event reporting by PTs (Trend) for Injury, Poisoning and Procedural Complications

Preferred Term	Number of Individual Cases
Toxicity To Various Agents	4,464
Overdose	1,625
Off Label Use	1,522
Intentional Overdose	1,437
Fall	1,195

Interpretation of results:

Most cases in this SOC were reported without specification of individual adverse events. The total fatal events accounted for less than 13.0% of the total events reported under this SOC. Most cases were reported by healthcare professionals. The age and sex distribution indicates that most cases were reported in

adults aged 18-64 years, with a higher number of females compared to males.

6.4 Gastrointestinal Disorders

In this SOC, most of the cases reported did not specify individual adverse events under the category of Gastrointestinal Disorders. The data indicates a significant number of cases across various age groups

and genders. The total fatal events accounted for less than 5% of the total events under this SOC.

Table 12 Pattern of adverse event reporting by PTs (Trend) for Gastrointestinal Disorders

Preferred Term	Number of Individual Cases
Diarrhoea	5,072
Nausea	3,240
Vomiting	3,204
Abdominal Pain	1,422
Abdominal Discomfort	1,112

Interpretation of results:

Most cases in this SOC were reported without specification of individual adverse events. The total fatal events accounted for less than 5% of the total events reported under this SOC. Most cases were reported by healthcare professionals. The age and sex distribution indicates that most cases were reported in adults aged 18-64 years and elderly population with age <65 yrs, with a higher number of females compared to males.

VII. CONCLUSION

This comprehensive analysis of metformin's adverse event reporting patterns from the FAERS database (1997-2025) provides valuable insights into the real-world safety profile of this widely prescribed antidiabetic medication. Our findings largely align with the established safety profile of metformin while highlighting several important trends in adverse event reporting.

The data reveals that gastrointestinal disorders remain among the most commonly reported adverse events, consistent with metformin's known side effect profile. However, the most frequently reported events fell under Metabolism and Nutrition Disorders, with lactic acidosis (n=11,613) being the predominant concern. This aligns with metformin's recognized rare but serious risk of lactic acidosis, particularly in patients with renal impairment.

Demographic analysis showed a slightly higher reporting rate in females (46.42%) compared to males (40.26%), with most cases occurring in elderly patients (≥65 years, 36.67%) and adults aged 18-64 years (34.99%). This age distribution reflects metformin's primary use in adult type 2 diabetes

patients, with particular vigilance needed in elderly populations who may have compromised renal function.

The temporal analysis revealed a significant increase in reporting from 2012 onward, peaking in 2020 (11.32% of total reports). This trend likely reflects improved pharmacovigilance systems and reporting rather than an actual increase in adverse events. The high proportion of healthcare professional reports (77.07%) suggests robust medical surveillance of metformin's safety profile.

Notably, 90.6% of reported events were classified as serious, with hospitalization (32.6%) being the most common serious outcome. While this appears concerning, it likely reflects reporting bias toward more severe cases rather than indicating that most metformin users experience serious adverse events.

These findings underscore the importance of continued vigilance regarding metformin's known risks, particularly lactic acidosis in vulnerable populations. Healthcare providers should maintain appropriate patient selection, dose adjustment based on renal function, and patient education about warning signs of serious adverse effects.

Limitations of this analysis include the inherent reporting biases in spontaneous adverse event databases, lack of exposure denominator data, and inability to establish causality. Despite these limitations, this comprehensive review provides valuable real-world evidence supporting metformin's overall favourable benefit-risk profile when used appropriately, while reinforcing the importance of established risk minimization measures.

Future pharmacovigilance efforts should focus on better characterizing risk factors for serious adverse events, particularly in special populations such as the elderly and those with renal impairment, to further

optimize the safe use of this essential antidiabetic medication.

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