Section: Pharmacology

Original Research Article

SAFETY PROFILE OF SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT-2) INHIBITORS - A RETROSPECTIVE PHARMACOVIGILANCE STUDY

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ABSTRACT

Background: Diabetes mellitus is a long-term disease that occurs when the body doesn't make enough insulin or doesn't use it right. The most common type is type 2 diabetes. The main reason for the incidence is probable unhealthy life style. SGLT2 inhibitors are a newer class of medications that reduce blood glucose levels by preventing renal reabsorption of glucose. But there are safety issues, like infections, ketoacidosis, and rare side effects like Fournier's gangrene. **Aim:** The study sought to assess the adverse drug reactions associated with Empagliflozin and Dapagliflozin, employing Individual Case Safety Reports obtained via a suspected ADR reporting format within the spontaneous reporting system from the ADR Monitoring Centre (AMC) of our Institution, under the Pharmacovigilance Programme of India (PvPI). **Materials and Methods:** A retrospective observational study was conducted using spontaneous Individual Case Safety Reports (ICSRs) collected through suspected Adverse Drug Reaction (ADR) reporting forms. All ICSRs related to Empagliflozin and Dapagliflozin reported between June 2019 and December 2024 were reviewed to assess the severity of adverse drug reactions (ADRs), patient characteristics, the system organ class (SOC), outcome of ADR, and the causality assessment. **Result:** A total of 73 ICSRs were analyzed, comprising 53 reports related to Empagliflozin and 20 related to Dapagliflozin. The proportion of male and female patients was almost identical, and the majority of ADRs were reported among middle-aged adults (45–60 years, n=33). Out of the 73 ICSRs, 60 Adverse drug reactions were considered non-serious and 13 were considered serious. In total, there were 87 ADRs, 63 from Empagliflozin and 24 from Dapagliflozin. The majority of ADRs were associated with Empagliflozin and which was related to skin and subcutaneous tissue disorders (n = 23), followed by renal and urinary disorders (n=15). Most of the adverse drug reactions (ADRs) to Dapagliflozin were skin and subcutaneous tissue disorders (n=10), and the next most common were infections and infestations (n=4). The 'outcome' of the ADRs were found to be 'recovering' (n=52) with no fatalities. As per WHO-UMC scale 63 ICSRs were under "probable" category. **Conclusion:** While spontaneous reporting aids in the detection of rare and unexpected adverse drug reactions (ADRs), its limitations highlight the imperative for rigorously designed prospective studies and improved pharmacovigilance practices in clinical settings.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycaemia resulting from impaired insulin secretion, defective insulin action, or a combination of both. Type 2 diabetes is the most prevalent type of diabetes in both industrialised and developing countries, rendering it a global health issue. Diabetes has been on the rise steadily over the past few decades. The International Diabetes Federation (IDF) says that there are currently 500 million people with diabetes around the world. By 2045, that number is expected to rise by 30%. Diabetes is a health problem that could become an epidemic and is spreading quickly, especially in countries with low and middle incomes, like India.[1,2] The main reason for this rise is that more and more people are overweight or obese and unhealthy lifestyle. There were roughly 77 million persons in India with diabetes in 2019. That number is predicted to grow to over 134 million by 2045. Diabetes is one of the 10 most prevalent causes of death in the world,

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along with heart disease (CVD), respiratory disease, and cancer.[3]

Diabetes mellitus is a multifactorial syndrome frequently associated with chronic complications impacting multiple organs, such as the eyes, kidneys, nerves, heart, and blood vessels. To lower the global and regional burden of diabetes, it is important to put in place good management and prevention plans. Oral antidiabetic drugs (OADs), insulin therapy, and non-insulin injectable therapy are all ways to treat diabetes mellitus. Biguanides, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins), glucagon-like peptide-1 receptor agonists (GLP-1RA), thiazolidinediones (glitazones), alpha-glucosidase inhibitors (AGIs), glinides (non-sulfonylurea insulin secretagogues like Repaglinide and Nateglinide), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are all types of oral antidiabetic agents.[4]

Gliflozins are the newest type of antidiabetic drugs to get approval from the Food and Drug Administration (FDA). They are sodium-glucose cotransporter-2 (SGLT2) inhibitors. The FDA has approved canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin as SGLT2 selective inhibitors to help adults with type 2 diabetes mellitus better control their blood sugar along with diet and exercise.(5) SGLT2 inhibitors work in a new way by lowering the amount of glucose that is reabsorbed by the renal tubules. This lowers blood glucose levels without causing insulin to be released. The FDA has approved these SGLT2 inhibitors for single, double, and triple therapy for type 2 diabetes mellitus. [6-9]

There is a lot of disagreement regarding how safe new drugs are, how often and how serious side effects are, and whether or not it is vital to make sure that new diabetes medications are safe and easy to take. The US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) have made new standards for the pharmaceutical business to follow. These rules say that new OADs should be tested for their risk of causing heart problems and that studies should be done to keep an eye on other potentially serious side effects, such as the higher risk of certain cancers and low blood sugar when taken with insulin or insulin secretagogues, genital mycotic infections, Fournier's gangrene,[7] urinary tract infections,[8] acute kidney injury, ketoacidosis,[9] volume depletion leading to low blood pressure, cardiovascular risks, lower limb amputation, and bone fractures.[10,11,12]

In real-world clinical settings, medicines are used differently than in controlled clinical trials. This is why continuous safety monitoring is necessary to keep the benefit-risk profile positive. Spontaneous reporting, where healthcare professionals notify regulatory authorities or pharmaceutical companies about suspected adverse drug reactions (ADRs), serves as a key method for monitoring drug safety. It facilitates the identification of previously unknown drug effects and the collection of real-world evidence, despite challenges such as underreporting. As a passive system, the role of healthcare professionals is crucial to enhance drug safety awareness. Recently, statistical tools have been created to find safety signals in large databases of spontaneous reports. However, these tools should only be used with other methods of assessing causality. [13-17]

Utilizing hospital-based ADR data from a tertiary care centre through suspected ADR reporting forms can provide valuable insights into the safety profile and potential risks of SGLT2 inhibitors. Enhancing patient care requires increasing awareness about ADR reporting. Therefore, identifying SGLT2 inhibitor–induced ADRs and implementing measures to minimize them are essential for improving patient adherence to treatment.

Aim: The study aimed to assess the adverse drug reactions caused by Empagliflozin and Dapagliflozin, employing Individual Case Safety Reports (ICSRs) collected via a suspected ADR reporting form within the spontaneous reporting system from the ADR Monitoring Centre (AMC) of our Institution, under the Pharmacovigilance Programme of India (PvPI).

Objectives

- To evaluate the incidence and prevalence of adverse drug reactions (ADRs) associated with Empagliflozin and Dapagliflozin.
- To evaluate the causality assessment of the adverse drug reactions associated with Empagliflozin and Dapagliflozin.

MATERIALS AND METHODS

A retrospective observational study was carried out utilising spontaneous Individual Case Safety Reports (ICSRs) data, adopting a suspected Adverse Drug Reaction (ADR) reporting format from AMC-Madras Medical College, Chennai. The information for an ICSR was collected utilising a suspected Adverse Drug Reaction Reporting form (ADR reporting form) from the Pharmacovigilance Programme of India (PvPI). The research included all Individual Case Safety Reports (ICSRs) of Empagliflozin and Dapagliflozin from June 2019 to December 2024, evaluated based on patient age group, gender, severity of Adverse Drug Reactions (ADRs), classification of ADRs by System Organ Class (SOC), reaction outcomes, and causality assessment (WHO-UMC scale) related to the suspected medications.

RESULTS

There were 73 ICSRs analysed during the study period: 53 from Empagliflozin and 20 from Dapagliflozin. The evaluation revealed that 37 ICSRs were associated with females and 36 with males. The majority of adverse drug reactions (ADRs) occurred in middle-aged adults (45–60 years old, n=33), followed by elderly individuals (61–75 years old,

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n=20), younger adults (19–44 years old, n=18), and finally, senile individuals (76–90 years old, n=2). (Figure 1).

Among the 73 ICSRs that were looked at, 60 ADRs were put into the "Non serious" category and 13 were put into the "Serious" category. Seven of the "Serious" ADRs were classified as "Disability," four as "Other medically important," and two as "Hospitalization-Initial/Prolonged." None were determined to be 'Fatal,' 'Life-threatening,' or 'Congenital anomaly'. (Table 1).

There were 87 ADRs linked to Empagliflozin and Dapagliflozin reported in 73 ICSRs and sorted by System Organ Class (SOC). Of the 87 ADRs, 63 were linked to Empagliflozin and 24 to Dapagliflozin. (Figure 2 and Figure 3).

The clinical manifestations of ADRs associated with Empagliflozin were analysed, with the majority classified as 'Skin and Subcutaneous disorders' (n=23), followed by 'Renal and Urinary disorders' (n=15), 'Reproductive and Breast disorders' (n=9), 'Endocrine disorders' (n=4), 'Infections and Infestations' (n=3), 'General disorders and Administration site conditions' (n=3), 'Nervous system disorder' (n=3), 'Metabolism and Nutrition disorders' (n=2), and 'Investigations' (n=1) as shown in. (Table 2).

The clinical manifestations of the ADRs associated with Dapagliflozin were examined, with the majority classified as ‘Skin and Subcutaneous disorders’ (n=10), followed by ‘Infections and Infestations’ (n=4), ‘Renal and Urinary disorders’ (n=4), ‘Reproductive and Breast disorders’ (n=3), ‘Gastrointestinal disorders’ (n=2), and ‘Metabolism and Nutrition disorders’ (n=1). (Table 3).

The outcome of the ADRs were assessed and found that most of them were "recovering" (n=52), followed by "recovered" (n=12), "unknown" (n=5), and "not recovered/continuing" (n=4). None of them were “fatal" or "recovering with sequelae" as shown in. (Figure 4).

Using the WHO-UMC causality assessment scale, we found that most ICSRs were rated as "Probable" (n=63), followed by "Possible" (n=10). None were classed as ‘Certain’, ‘Unlikely’, ‘Unclassified’, or ‘Unassessable’ as shown in. (Figure 5)

Table 1: Seriousness of the ADRs reported

Seriousness criteria		Number of ICSRs
Serious ADRs	Death	0
	Life threatening	0
	Hospitalization/Prolonged hospital stay	2
	Disability	7
	Congenital anomaly	0
	Other medically important	4
Non serious ADRs		60

Table 2: Clinical manifestations of ADRs due to Empagliflozin

System Organ Class (SOC)	Low Level Term (LLT)	No. of ICSRs
Reproductive system & Breast disorders	Penile ulcer	3
	Penile fissure	2
	Balanoposthitis	3
	Scrotum swelling	1
Investigations	Weight loss	1
Renal and Urinary disorders	Dysuria	10
	Polyuria	1
	Increased Frequency of micturition	1
	Burning micturition	3
Endocrine disorders	Euglycemic ketosis	4
Nervous system disorders	Giddiness	1
	Fainting	1
	Tingling sensation	1
General disorders and administration site conditions	Tiredness	1
	Fatigue	2
Metabolism & nutrition disorders	Hypoglycaemia	2
Infections & Infestations	Urinary tract infection	1
	Epididymo-orchitis	1
	Prostatic abscess	1
Skin and Subcutaneous disorders	Genital itching	19
	Pruritus vulvae	3
	Penile itching	1

Table 3: Clinical manifestations of ADRs due to Dapagliflozin

System Organ Class (SOC)	Low Level Term (LLT)	No. of ICSRs
Skin and Subcutaneous disorders	Genital itching	9
	Pruritus vulvae	1
Infections & Infestations	Genitourinary infection	3
	Urinary tract infection	1
Renal and Urinary disorders	Polyuria	1
	Increased urination	1
	Burning micturition	1

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	Haematuria	**1**
Reproductive system & Breast disorders	**Penile fissure** **Penile discharge** **Balanoposthitis**	**1** **1** **1**
Gastrointestinal disorders	**Indigestion** **Lower abdominal pain**	**1** **1**
Metabolism & nutrition disorders	**Hypoglycaemia**	**1**

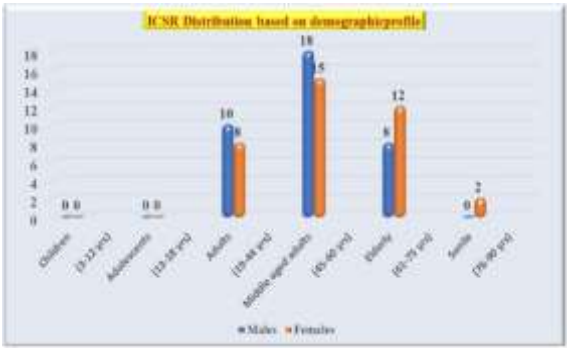

Figure 1: ICSR distribution based on demographic profile

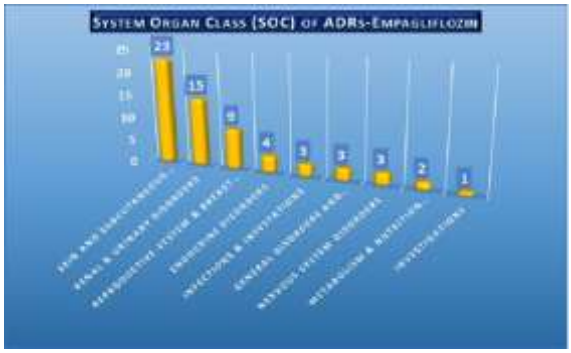

Figure 2: System Organ Class of ADRs due to Empagliflozin

Figure 3: System Organ Class of ADRs due to Dapagliflozin

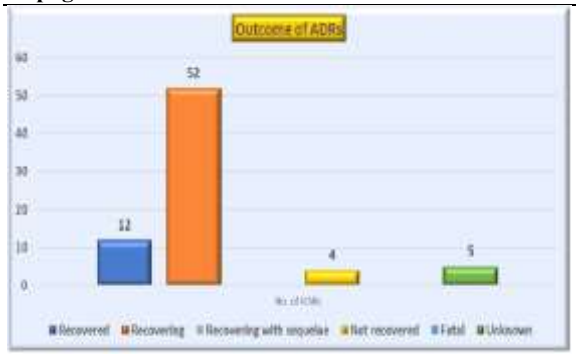

Figure 4: Outcome of the ADRs

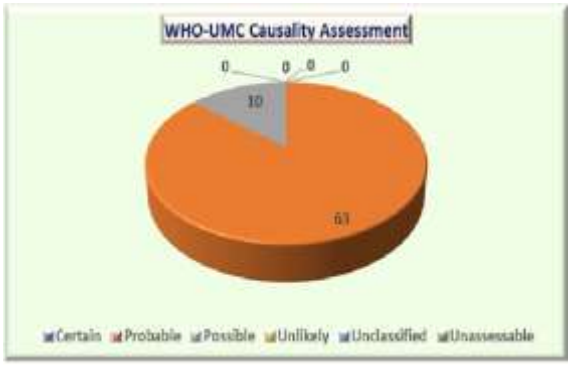

Figure 5: Causality assessment of ADRs based on WHO-UMC scale

DISCUSSION

The study examined 73 ICSRs, comprising 53 associated with Empagliflozin-induced ADRs and 20 linked to Dapagliflozin-induced ADRs. After evaluation, most of the cases were reported in females (n=37) rather than males (n=36). The majority of adverse drug reactions (ADRs) were observed in the middle-aged adults (45–60 years) (n=33). Out of the 73 ICSRs evaluated, 13 were classified as 'Serious' ADRs. The majority of these serious ADRs were categorised as 'disability' (n=7).

There were 87 ADRs linked to Empagliflozin and Dapagliflozin reported in the 73 ICSRs. Of these 87 ADRs, 63 were linked to Empagliflozin and 24 to Dapagliflozin. Most of the ADRs that were caused by either Empagliflozin or Dapagliflozin were categorised as "Skin and Subcutaneous disorders" under System Organ Class (SOC).

The outcome of the ADRs were found to be in the "recovering"(n=52) group. The WHO-UMC causality assessment scale was used to establish the causal relationship between the drug & ADR combinations and found that most of them were in the "probable" category (n=63).

The reported gender difference was negligible, with only one ADR count higher in females (n=37) compared to males (n=36). This indicates that both sexes are nearly equally vulnerable to adverse drug reactions related to Empagliflozin and Dapagliflozin. In our study, the prevalence of ADRs was marginally higher in females, consistent with the prior research conducted by Goldman et al.[18] Our study revealed that most ADRs occurred among 'Middle aged adults' (45-60 years), whereas the study by Goldman et al,[18] identified the majority of ADRs in the 'Adults' category (<75 years). Our research indicated that the majority of the adverse drug reactions (ADRs) were classified as 'Non-Serious' rather than 'Serious' based on established seriousness criteria.

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Our study identified the primary adverse drug reactions (ADRs) associated with Empagliflozin: 'Genital itching,' categorised under 'Skin and Subcutaneous disorders'; 'Dysuria,' classified under 'Renal disorders'; and 'Euglycemic ketosis,' placed within 'Endocrine disorders.' Our study findings diverge from those of K. Kaku et al,[19] where the primary adverse drug reactions (ADRs) identified were 'urinary tract infections,' succeeded by 'excessive/frequent urination.'

Most of the ADRs caused by Dapagliflozin were also "Genital itching," which is a type of "Skin and Subcutaneous disorders," and "Genitourinary infection," which is a type of "Infections and Infestations." These results contrast with those of the study by Z. Zhou et al,[20] where the primary adverse drug reactions (ADRs) included 'Diabetic ketoacidosis', 'Ketoacidosis', and 'Euglycaemic diabetic ketoacidosis' classified under the SOC of 'Metabolism and Nutrition disorders', followed by 'Fourniers gangrene' categorised under the SOC of 'Infections and Infestations'.

The variations between our study findings and those of previous studies may be attributed to demographic, genetic, and nutritional differences, as well as potential drug–drug interactions observed in these ICSRs.

Strengths and limitations: This study utilises the suspected ADR reporting format of ICSRs, which provides extensive real-world data on ADRs.

The study was based on spontaneous reporting systems, which have inherent limitations such as underreporting, reporting bias, and incomplete data. Additionally, it did not assess drug–drug interactions, comorbidities, or other factors that may have contributed to the occurrence of adverse drug reactions (ADRs).

CONCLUSION

This study aimed to evaluate the adverse drug reactions (ADRs) experienced by patients with type 2 diabetes mellitus who were treated with Empagliflozin and Dapagliflozin. The suspected ADR reporting format from spontaneous reporting systems was utilized for data collection. Only minor differences in ADR patterns were observed between male and female patients, indicating that skin and subcutaneous tissue disorders were the most commonly affected systems for both drugs. According to the WHO-UMC causality assessment scale, most ADRs were classified as "non-serious" and fell under the "Probable" category.

Spontaneous reporting of adverse drug reactions (ADRs) aids in the detection of new and uncommon ADRs that could not be identified during clinical trials. However, given the inherent limitations of spontaneous reporting data, there remains a need for well-designed prospective studies and effective utilization of the pharmacovigilance system in clinical practice.

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Disclaimer: The data were analysed utilising Individual Case Safety Reports of suspected Adverse Drug Reactions (ADRs) from the spontaneous reporting system at the ADR Monitoring Centre (AMC) - Madras Medical College, Chennai. The probability that the suspected reaction is drug-related varies across cases in this study. The authors of this study express their opinions, which do not reflect the views of NCC-PvPI, its scientific committee, or other regulatory bodies.

Ethics Approval: Institutional ethics approval is waived as the data analysed in the study is from anonymised data management system

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