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EVOLVING SAFETY CONCERNS ASSOCIATED WITH ANTI-DIABETIC DRUGS

Roma Ghai, Kiran Sharma *, Manisha Prajapati, Ishani Verma, Jaskaran Singh, Harsh Bansal and K. Nagarajan

KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad, affiliated to Dr. A.P.J. Abdul Kalam Technical University, Lucknow – 201206, Uttar Pradesh, India.

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Correspondence to Author:
Kiran Sharma

Assistant Professor,
KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad, affiliated to Dr. A.P.J. Abdul Kalam Technical University, Lucknow – 201206, Uttar Pradesh, India.

E-mail: kiran.sharma@kiet.edu

ABSTRACT: Diabetes Mellitus, a chronic metabolic disorder, is prevalent all over the world nowadays. As a result, it is estimated that it can become an epidemic in some parts of the world soon. The number of affected people could be as double as that of the currently affected patients till the next decade. In order to fulfill the increasing demands of newer, safer, and more effective medications for treatment, prevention, diagnosis, and mitigation of this condition, companies all over the world are trying to introduce new medications in the market. Before entering the market, any new drug undergoes several clinical trials and tests to check and ensure its safety and efficacy. All the associated Adverse Drug Reactions are supervised and monitored by Pharmacovigilance Centers. This ensures that the patients receive safe and effective treatment with minimum or no undesired effects. A brief overview of commonly used hypoglycemic agents and their associated ADRs obtained from publishing data is elucidated in this review.

INTRODUCTION: Diabetes Mellitus (DM) could be explained as a metabolic disorder, in chronic state. It is characterized by increased blood sugar levels, which could lead to serious damage of heart, blood vessels, kidneys, nerves and other vital organs of body. Type 1 diabetes is a type of disease that is autoimmune. The immune system attacks and kills the beta cells (Langerhans islets) of the insulin-producing pancreas. Type 2 diabetes occurs when the cells of body become resistant to insulin and do not metabolize the sugars and thus it builds up in the blood which allows a rise in blood glucose levels.

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Gestational diabetes is referred to high blood glucose levels during pregnancy [1]. About 422 million people globally suffer from diabetes, with the majority living in low-and middle-income countries, and 1.6 million deaths per year are directly attributed to diabetes. Over the past few decades, both the number of cases and the incidence of diabetes have been gradually growing.

An internationally accepted goal is to halt the growth in diabetes and obesity by 2025 [2]. In the world, one out of six people with diabetes is from India. The statistics position the nation among the top 10 countries for people with diabetes, with an estimated 77 million diabetics coming in at number two. China tops the list with over 116 million diabetics [3]. Adverse Drug Reactions (ADR) could be explained as undesirable and harmful effects produced by a drug administered in therapeutic concentrations for treatment, mitigation, or diagnosis of any ailment [4].

ADR has been recognized as a major limitation in providing health care4.ADRs are responsible for frequent hospital admissions and a major cause of morbidity. In a study done in Indian ambulatory patients, it was pointed out that 3.4-7% of hospitalization was due to ADR [5]. Before launching a new drug in the market; it undergoes clinical trials and strict surveillance in order to ensure its safety. ADRs, if any, should be reported to monitoring centers and awareness should be developed among patients about them [5]. ADR reporting prevents the serious adverse effects and aids in instructing healthcare providers for better management of ADRs [6]. Pharmacovigilance is a branch of science that deals with ADR recognition and their reporting [7]. Drugs commonly used for the treatment of Diabetes Mellitus are Sulphonylureas (glimepiride, gliclazide *etc.*), Biguanides (metformin), Alpha- glucosidase Inhibitors (acarbose, voglibose), Phenylalanine analogues/Meglitinides (repaglinide, nateglinide), Dipeptidyl peptidase-4 inhibitors (sitagliptin, teneligliptin, saxagliptin etc.), Sodium-glucose Cotransporter-2 Inhibitors (dapagliflozin, Canagliflozin), Glucagon-like peptide-1agonists (exenatide, lixisenatide, dulaglutide, liraglutide *etc.*), Thiazolidinediones (pioglitazone, rosiglitazone) [8]. Some advancement has resulted in introduction of new anti-diabetic agents. These latest agents are Glucokinase Activator (Piragliatin), Dual PPAR Agonists (Aleglitazar), Monoclonal Antibodies (Otelixizumab, Teplizumab), Dopamine-2 Receptor Agonist (Bromocriptine) [9]. This review throws an insight on the mechanism of action as well as examples of adverse drug reaction reported, as researched from various journal databases. The review has been compiled after searching journals from Google Scholar, Science Direct, Pubmed, Cochrane Library, *etc.* The keywords used in surfing the data were Anti-diabetic agents, Hyperglycemia, Diabetes Mellitus, and adverse drug reactions.

Management of Diabetes Mellitus: The categories of Anti-diabetic agents used for management of DM-2 are represented below with examples of Adverse Drug Reactions

Sulphonylureas: Sulphonylureas were discovered in 1942. This class of drugs represents a group of anti-hyperglycemic agents primarily used in the treatment of T1DM.Sulfonylurea increases insulin release by binding to a subunit of potassium ATP-dependent channels known as the sulfonylurea receptor. The frequent side effect identified with sulfonylurea administration is hypoglycemia. Chlorpropamide, tolazamide, and tolbutamide are included in first-generation sulfonylurea, while glipizide and gliclazide are included in second-generation sulfonylurea [10]. Tolbutamide is more likely to cause adverse effects, such as jaundice, compared to second-generation sulfonylureas [11]. Glimepiride is a third-generation sulfonylurea approved in 1995 by FDA, long-acting, with hypoglycemic activity. Glimepiride is very potent and has a longer duration of action compared to other generations of sulfonylurea compounds [12, 13]. The first-generation sulphonylureas are no longer used due to associated adverse effects [14]. Although second and third-generation Sulfonylureas are effective and safe comparatively there are certain ADRs associated with them. Some case reports of drugs like Glimepiride, Glipizide, Gliclazidehave been reported in published database, and these examples are given in **Table 1**.

TABLE 1: ADRS DETECTED ALONG WITH STATUS OF SOME SULPHONYLUREAS CLASS OF DRUGS

Name of Drug	ADR detected	Evidence	Age/ Gender	Status
Glimepiride	Cholestasis &progressive jaundice	Case report	58/ Male	Glimepiride was discontinued; insulin therapy was started [15]
Glimepiride	Vasculitis	Case report	72/ Female	Glimepiride was discontinued. Within 1 week all lesions were healed spontaneously [16]
Glipizide	Hepatotoxicity	Case report	71/ Female	Discontinuation of glipizide showed improvement [17]
Glipizide	Proximal myopathy	Case report	61/Male	The symptoms of myopathy improved by itself after stopping glipizide [18]
All Sulphonylureas	Increased risk of Myocardial Infarction and severe hypoglycemia	Cohort Study	40+/Male & Female	The patients were hospitalized for their symptoms of MI, severe hypoglycemia, ischemic stroke [19]

Biguanides: Metformin, Phenformin and Buformin compose the biguanide class of anti-diabetic drugs. Metformin and Phenformin were first described in 1957 followed by Buformin in 1958. Owing to the high risk of lactic acidosis in the 1970s, Phenformin and Buformin were removed from the market for clinical use 20. Metformin, approved by the FDA in 1994, is a type 2 diabetes mellitus antidiabetic agent. Blood glucose levels are decreased by decreasing the production of glucose in the liver, decreasing intestinal absorption, and increasing insulin sensitivity. Metformin reduces blood glucose in both basal and postprandial blood [21]. Some ADR case studies of Metformin have been reported in the published database. So, examples are given in **Table 2**.

TABLE 2: ADRS DETECTED ALONG WITH STATUS OF SOME BIGUANIDES CLASS OF DRUGS

Name of Drug	ADR detected	Evidence	Age/ Gender	Status
Metformin	Lactic Acidosis	Case study	82/Male	Metformin was stopped and treated with dextrose, crystalloids, and bicarbonate intravenously, and urgent hemodialysis was performed [22]
Metformin	Cholestatic hepatitis	Case report	68/ Male	Metformin was discontinued [23]
Metformin	Vitamin B 12 deficiency and Anemia	Phase 3 clinical trial	25+/ Male & Female	Vitamin B12 was administered to correct the deficiency and continuous monitoring was conducted [24]
Metformin	Hypersensitivity reaction	Case report	59/Female	Metformin was discontinued and patient was prescribed Fexofenadine, Montelukast, Levocetrizine combination to treat the reaction [25]
Metformin	Gastrointestinal problems (diarrhea, nausea, vomiting, pain abdomen, flatulence, retching, dysgeusia)	Cross-sectional study	52.8±11.9 years/ 70 male & 50 female	ADR got removed with the use of extended-release formulation [26]

Alpha-glucosidase Inhibitors: The members of this class were approved during the 1990s; they inhibit the intestinal alpha-glucosidase and alpha-amylase of pancreas by reversible and competitive inhibition [27]. The degradation of larger carbohydrates into glucose is stopped and the increase in postprandial blood glucose levels decreases. This results in a smaller and slower increase in blood glucose levels after meals, which is successful during day [28]. Members of this class are Acarbose, Miglitol and Voglibose [29]. Some case reports of Acarbose, Voglibose and Miglitol have been reported in published database, examples are given in the **Table 3**.

TABLE 3: ADRS DETECTED ALONG WITH STATUS OF SOME SOME ALPHA-GLUCOSIDASE INHIBITORS CLASS OF DRUGS

Name of Drug	ADR detected	Evidence	Age/Gender	Status
Acarbose	Hepatotoxicity	Case report	57/ Female	Acarbose was Discontinued [30]
Voglibose	Hepatic necrosis with cholestasis	Case report	76/ Female	Voglibose was discontinued [31]
Voglibose	Severe Dizziness	Case report	75/ Male	Voglibose was discontinued (dizziness persisted) [32]
Miglitol	Hallucinations	Case report	71/ Male	Miglitol was discontinued [33]

Meglitinides: Meglitinides are a class of oral antidiabetic agents approved by US FDA in 1997, which increase the secretion of insulin in the pancreas [34]. Because of this, they are often referred to as "insulin secretagogues." In reaction to a meal, insulin secretion is enhanced but does not appear to be intensified during fasting periods. Because meglitinides increase insulin secretion, low blood sugars, i.e. hypoglycemia, can be induced [35]. Two analogues are currently available for clinical use, Repaglinide and Nateglinide [36]. Repaglinide is absorbed quickly and has a fast onset and short time of action. In the liver, CYP2C8 and CYP3A4 are metabolized, and their metabolites are excreted in the bile. Nateglinide was approved in 2000 and is metabolized by the CYP2C9 isoenzyme cytochrome P450 and, to a lesser degree, by CYP3A4. The parent drug and metabolites are excreted primarily in the urine [37, 38]. Some case reports of Repaglinide and Nateglinide have been reported in published database, examples are given in **Table 4**.

TABLE 4: ADRS DETECTED ALONG WITH STATUS OF SOME MEGLITINIDES CLASS OF DRUGS

Name of Drug	ADR detected	Evidence	Age/ Gender	Status
Repaglinide	Hypoglycemia	Case Study	67/ Male	Repaglinide was discontinued [39].
Repaglinide	Thrombocytopenia	Case report	71/Male	Discontinuation of repaglinide increase platelet count [40].
Nateglinide	Leukocytoclastic angiitis	Case Report	55/ Male	Nateglinide was discontinued and Prednisone was given for management of ADR [41].

Thiazolidinediones: Glycemic management and insulin resistance are supported by thiazolidinediones, also called glitazones. Rosiglitazone and Pioglitazone were approved in 1999 by FDA [42, 43]. Although, Rosiglitazone was banned due to increased risk of heart attack and stroke in 2010 [44]. Pioglitazonewas banned in India in 2013 due to some evidence of associated bladder cancer, but it was revoked after 1.5 months [45]. Troglitazone is the prototype drug in this class introduced in 1996, but due to its association with idiosyncratic hepatotoxicity, it was removed from the market in March 2000 [46]. They activate the Peroxisome Proliferator-Activated Receptor gamma (PPARgamma) nuclear receptor, altering the expression of the glucose and lipid homeostasis genes involved. PPARgamma stimulation increases insulin sensitivity through several pathways, such as increased GLUT4 glucose transporter expression, the development of smaller and more insulin-sensitive adipocytes, *etc.* [47] Some case reports of Pioglitazone and Rosiglitazone have been reported in published database, examples are given in the **Table 5**.

TABLE 5: ADRS DETECTED ALONG WITH STATUS OF SOME THIAZOLIDINEDIONE CLASS OF DRUGS

Name of Drug	ADR Detected	Evidence	Age/ Gender	Status
Pioglitazone	Pleural Effusion	Case Report	76/ Female	Pioglitazone was discontinued [48].
Pioglitazone	Congestive Heart Faliure and Pulmonary Edema	Case report	65/ Male	Pioglitazone was discontinued [49].
Rosiglitazone	Hepatocellular injury	Case report	61/ Male	Rosiglitazone was discontinued [50].
Rosiglitazone	Severe electrolyte imbalance and edema	Case report	49/ Male	Rosiglitazone was discontinued [51].

DPP-4 Inhibitors: DPP-4 inhibitors also known as gliptins, are a class of oral diabetic medicines approved for the treatment of type 2 diabetes mellitus in adults by the Food and Drug Administration (FDA) in 2006 [52]. Sitagliptin, Saxagliptin, Linagliptin, currently followed by Alogliptin approved in 2013 by FDA, compose this category of anti-diabetic agents [53]. The approval of Vildagliptin is from the European Medicines Agency (EMA), but not from the FDA [54]. DPP-4 inhibitors increase the concentrations of active incretin hormones, GLP-1, and glucose-dependent insulinotropic polypeptides (secreted by enteroendocrine L and K cells, substrates for DPP-4). This results in an enhanced response of β-cells to prevailing glucose levels and in the suppression of glucagon secretion [55]. All agents in this class, alone or in conjunction with other hypoglycemic agents, are used in conjunction with diet and exercise [56]. However, case reports of agents of this class have been reported in the published database; examples are given in **Table 6**.

TABLE 6: ADRS DETECTED ALONG WITH STATUS OF SOME DPP-4 INHIBITORS CLASS OF DRUGS

Name of Drug	ADR detected	Evidence	Age/ Gender	Status
Vildagliptin	Bullous pemphigoid	Case report	61/ Male	Vildagliptin was discontinued and bolus insulin was given [57]
Sitagliptin	Arthralgia	Case report	56/ Female	Sitagliptin was discontinued [58]
Sitagliptin	Rheumatoid Arthritis	Case report	56/ Male	Sitagliptin was discontinued [59]
Saxagliptin	Acute Pancreatitis	Case report	85/ Female	Status not specified; Saxagliptin was highly suspected [60]
Alogliptin	Angioedema	Case report	67/Male	Alogliptin was stopped and intravenous steroids and antihistamines resolved the problem [61]
Linagliptin	Blistering and ulceration	Case report	60/Male	Linagliptin was stopped and intravenous tazocin and teicoplanin was given [62]

SGLT2 Inhibitors: Sodium-glucose co-transporter 2 (SGLT2) inhibitors, also known as Gliflozin, are a new class of diabetic drugs indicated for the treatment of type 2 diabetes. The first member of this class, Canagliflozin was approved in 2013 [63]. They are also found to have cardiac advantages in patients with diabetes and are being studied for possible use in type 1 diabetes. They act by reducing the absorption of glucose through the kidneys so that excess glucose is excreted by urination.SGLT2 is a protein in humans that makes it easier to reabsorb glucose in the kidney. SGLT2 inhibitors block the reabsorption of glucose by the kidney, increase glucose excretion and decrease blood glucose levels [64]. Currently, the Food and Drug Administration (FDA) has approved three SGLT2 selective inhibitors for mono, dual, and triple therapy: canagliflozin (2013), dapagliflozin (2014), and empagliflozin (2014) [65]. In January 2020, the FDA approved an extended-release combination product containing empagliflozin, metformin, and linagliptin [66]. The case reports of agents of this class have been reported in published database, examples are given in **Table 7**.

TABLE 7: ADRS DETECTED ALONG WITH STATUS OF SOME SGLT2 INHIBITORS CLASS OF DRUGS

Name of Drug	ADR detected	Evidence	Age/ Gender	Status
Empagliflozin	Diabetic ketoacidosis	Case report	47/ Male	Empagliflozin was discontinued [67]
Empagliflozin	Fournier's gangrene (Serious infection in genital area)	Case report	57/ Male	The patient required two surgical interventions with hyperbaric oxygen therapy and all oral medications were stopped [68]
Empagliflozin	Cutaneous Polyarteritis Nodosa	Case report	69/Male	Upon cessation of empagliflozin problem resolved [69]
Canagliflozin	Genital mycotic infections, UTI, osmotic diuresis, and reduced intravascular volume	Case report	54/ Male	Patient required insulin infusion (up to 10 units/hr) along with dextrose to prevent hypoglycemia for 72 hours to normalize the anion gap and clear the ketones [70]
Canagliflozin	Diabetic Ketoacidosis	Case report	62/Female	Canagliflozin was discontinued and an insulin drip initiated [71]
Dapagliflozin	Pancreatitis.	Case report	51/ Male	Dapagliflozin was discontinued [72]

Glucagon-like Peptide- 1 Receptor Agonist: For the treatment of type 2 diabetes mellitus in adults, GLP-1 agonists were approved by FDA in 2019 [73]. Exenatide, Lixisenatide, Liraglutide, Albiglutide, Dulaglutide, and Semaglutide are the agents in this class. It has been shown that these agents decrease HbA1C (by 0.8-1.6 percent), body weight (by 1-3 kg), blood pressure, and lipids. GLP-1 receptor agonists are associated with a low risk of hypoglycemia and the most common adverse effects are linked to the GI tract [74]. However, case reports of agents of this class have been reported in the published database; examples are given in Table 8.

TABLE 8: ADRS DETECTED ALONG WITH STATUS OF SOME GLUCAGON-LIKE PEPTIDE- 1 RECEPTOR AGONIST CLASS OF DRUGS

Name of Drug	ADR Detected	Evidence	Age/ Gender	Status
Liraglutide	Pancreatitis	Case report	53/ Male	Liraglutide was discontinued [75]
Exenatide	Systemic Allergic Reaction	Case report	52/ Male	Exenatide was discontinued [76]
Abliglutide	Edema	Case report	35/ Female	Albiglutide was discontinued [77]

CONCLUSION: With the introduction of new oral anti-diabetic medications in the market, the need for ADR monitoring is extremely important in order to maintain safety and efficacy throughout the treatment. Though the recently approved classes, GLP-1 agonists and SGLT-2 inhibitors, have proved to be beneficial, they also have the potential to cause ADRs like pancreatitis, edema, allergic reactions and ketoacidosis, Fournier's gangrene, mycotic infections, respectively. The older classes, such as Thiazolidinediones, were associated with life-threatening conditions like Hepatocellular injury and heart failure, hence were withdrawn from the market permanently. In other categories, the most reported ADRs were hepatotoxicity, pancreatitis, electrolyte imbalance, arthritis, *etc.* This brings us to the conclusion that active and effective ADR monitoring is necessary, followed by its awareness among healthcare profession.

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