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Review article *Medical research*

A review on adverse drug reactions of antidiabetic drugs

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ABSTRACT

India had 69.2 million people living with diabetes (8.7%) as per the 2015 data by WHO. of these, it remained undiagnosed in more than 36 million people. Effective management of diabetes and an adverse effect of drugs is associated with lower morbidity, mortality, and health care. Over time, high blood sugar can seriously compromise every major organ system in the body, causing heart attacks, strokes, nerve damage, kidney failure, blindness, impotence and infections that can lead to amputations. Treatment for diabetes includes insulin and oral antidiabetic agents. Along with these drugs, diabetic patients generally take medications to treat dyslipidemia, an antihypertensive drug, and antiplatelet therapy. Adverse drug reaction associated with antidiabetic treatment are hypoglycemia, hypoglycemic coma, hypersensitivity, hepatotoxicity, drug induced erythema multiforme, photodermatitis etc. So, it is need of the new era to aware people about the adverse effects of an antidiabetic drug. It is necessary to educate the patient on their medications and potential adverse events associated with each medication to limit potential treatment complications. The main objective of the article is to increase awareness about the drugs used in diabetes treatment, its consequences, and adverse drug reaction reporting.

Keywords: *Diabetes, Antidiabetic agents, Adverse drug reaction, Adverse drug reaction reporting*

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder mainly characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are the important characteristic of these defects in insulin secretion or insulin action. The disease may give rise to multiple complications such as cardiovascular disease, nerve damage, kidney damage, eye damage, foot ulcer, liver damage etc., and in severe cases, coma. Patients must receive long-term treatment to maintain the stability in blood sugar, thereby reducing the risk of complications [1, 2].

MAJOR CLINICAL FEATURES [2]

1. Polyuria- The need to urinate frequently
2. Polydipsia-Increased thirst & fluid intake

3. Polyphagia-Increased appetite
4. Weight loss

Antidiabetic drugs

Antidiabetic drugs are developed to stabilize and control blood glucose levels amongst diabetes patient. Antidiabetic drugs are commonly used to manage diabetes [3, 4].

Table 1: Antidiabetic drug class

Sr. No.	Class	Brands	Dosage forms	Mechanism Of Action
1.	Sulfonylurea	Glyburide, Glimepiride Glipizide	Oral tablets	Stimulating insulin release by pancreatic beta cells by inhibiting the K_{ATP} channel
2.	Biguanides	Metmorphin	Oral tablets	Acts on the liver to reduce gluconeogenesis and decrease in insulin resistance via increasing AMPK signaling.
3.	Alpha-glucosidase inhibitor	Acarbose, Miglitol, Voglibose	Oral tablets	Reduces glucose absorbance by acting on small intestine to cause decrease in production of enzymes needed to digest carbohydrate
4.	Thiazolidinediones	Pioglitazone Rosiglitazone	Oral tablet	Reduce insulin resistance by activating PPAR-γ in fat and muscle
5.	Amaryl mimetics	Pramlintide	Injectable solution subcutaneous	Prolong gastric emptying and postprandial glucagon secretion and suppresses appetite
6.	Dipeptidyl Peptidase-4 Inhibitors	Vildagliptin Sitagliptin Linagliptin Alogliptine	Oral tablet	Dipeptidyl peptidase-4 (DPP-4) inhibitors increase blood concentration of the incretin GLP-1 by inhibiting its degradation by dipeptidyl peptidase-4

Marketed antidiabetic drugs

Some examples of antidiabetic drugs commonly used in diabetes therapy

Table 2: List of marketed antidiabetic drugs

Brand Name	Generic Name	Drug Form	Type	Drug Class	Made By	Drug Description
Actos	Pioglitazone	Tablet	2	Thiazolidinediones	Takeda	Acts by reducing insulin resistance.
Actrapid	Insulin soluble human	Injection solution	1 2	Insulin	Novo Nordisk Ltd	Used as a substitute for the body's insulin in people with diabetes.
Amaryl	Glimepiride	Tablet	2	Sulphonylureas	Sanofi-Aventis	Acts by boosting the body's insulin sensitivity.
Apidra	Insulin Glulisine	Injection solution	1 2	Insulin	Sanofi-Aventis	Fast acting, mealtime insulin used to help maintain blood sugar control for adults and children (4 years and older)

Gliclazide	Gliclazide	Tablet	2	Sulphonylureas	Servier Laboratories	that works mainly by boosting the amount of insulin produced by the pancreas
Januvia	Sitagliptin phosphate monohydrate	Tablet	2	DPP-4 inhibitors (Gliptins)	Merck Sharp & Dohme	Oral type 2 diabetes medication which works by increasing the amount of incretin hormones in the body that help control blood sugar.
Metformin	Metformin hydrochloride	Tablet	2	Biguanides	Takeda Pharmaceuticals	Oral antidiabetic medication considered as the first-line of drug treatment for patients with type 2 diabetes, particularly those who are also overweight or obese.

Adverse drug reaction

(ADR). Any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy. This excludes therapeutic failures, intentional and accidental poisoning and drug abuse. The study of ADRs is the concern of the field known as pharmacovigilance [5].

Table 3: Classification of adverse drug reaction

Sr. No.	Classification of ADR	Features	Examples
1	Type A (Augmented and predictable)	Relatively common Pharmacologically predictable Dose-dependent. Improves if the medicine banned.	Hypoglycemia with sulfonylureas Bradycardia with beta blockers, etc.
2	Type B (*Bizarre* or unpredictable)	Involves interaction with a microorganism Dose-independent Pharmacologically predictable	Dental caries with sugar coated tablets Resistance due to overuse of any one antibiotic, etc.
3	Type C (Chemical)	Related to drug concentration An irritant reaction	Extravasation reactions Phlebitis, etc.
4	Type D (Delivery)	Caused by method of administration or nature of formulation Improves if the medicine is withdrawn or method of delivery changed.	Inflammation or infection around implant particles Infection at the site of injection, etc.
5	Type E (Exit)	Pharmacologically predictable Begins only when the medicine is stopped or dose is reduced Improves if medicine is reintroduced	Withdrawal reactions due to opioids, benzodiazepines, clonidine, beta blockers, etc.
6	Type F (Familial)	occurs only in the genetically predisposed	Hemolytic anemia with primaquine in G6PD deficient individuals, etc.
7	Type G (Genotoxicity)	causes irreversible genetic damage	Teratogenic agents
8	Type H	Requires activation of immune	Anaphylaxis with penicillin

	(Hypersensitivity)	system Improves if medicine is withdrawn	allergic skin reactions with antimicrobial agents, etc.
9	Type U (Unclassified)	Mechanism not understood	Taste disturbances with simvastatin, Nausea, and vomiting with gaseous anesthetic, etc.

Adverse drug reaction reporting

Analysis of adverse drug reaction reports is the way to monitor the safety of medicines. There is the potential for an adverse drug reaction to occur with the use of any medicine or vaccine – whether it is supplied on prescription, over-the-counter or as complementary medicine. When a medicine or vaccine is first registered and made available for use, information about its safety and efficacy is usually available only from clinical trials. Post-marketing surveillance of the marketed medicines and vaccines contributes to a better understanding of their possible adverse drug reactions when medicines are used outside the controlled conditions of clinical trials [6, 7, 8, 9].

Figure 1: ADR reporting and monitoring procedure

Table 4: Details required for reporting ADR events

Contents in ADR reporting	Information	Others
Content of reports	Adverse reactions to the drug, suspected drug's details, patient's information	Medications overdose, pharmaceutical defect, drug interactions
Role in reporting adverse drug reaction	medical practitioners or healthcare professionals, doctors, nurses, pharmacists, assistants, pharmaceutical technicians, pharmaceutical assistants, clinical officers and other health care providers	Manufacturers, all government, and private hospital's health center
When to report	Any adverse reactions if noticed should be reported.	–
Reporting form	Through filled yellow card form	–
Reporting authority	Fully filled ADR form should be submitted to pharmacovigilance center	–

Clinical trials

Clinical trials involving new drugs are commonly classified into five phases. Each phase in the new drug approval process is treated as a separate clinical trial. The drug-development process will proceed through all four phases. If the drug in the clinical trial successfully passes through phases 0, 1, 2, and 3, it will usually be approved by the national regulatory authority for therapeutic use. Before pharmaceutical industries start clinical trials on a drug, they will also have conducted preclinical studies. Each phase of the clinical trial has a different purpose and helps scientists answer a different question [10, 11].

- Phase I – Study of pharmacokinetics and pharmacokinetics in humans.
- Phase II - Establishing the efficacy of the drug.
- Phase III - Final confirmation of safety and efficacy of the drug.
- Phase IV – Post-marketing surveillance

Antidiabetic drugs reported adverse drug reaction

Adverse events associated with antidiabetic treatment are hypoglycemia, hypersensitivity, hypoglycemic coma, hepatotoxicity, drug induced erythema multiforme, photodermatitis etc. So, it is need of the new era to aware people about the adverse effects of an antidiabetic drug [12, 13, 14, 15].

Table 5: Antidiabetic drugs and reported ADR

Class of antidiabetic drug	Example	Dosage form	Reported ADR
Thiazolidinedione antidiabetic	Actos	Tablet	Upper respiratory tract infection, headache, sinusitis, Myalgia, Tooth disorder, pharyngitis
Human insulin analog	Apidra	Subcutaneous injection solution	Nasopharyngitis, Upper respiratory tract infection, headache, influenza, Vomiting, Cough, ear infection, abdominal pain
Sulfonylurea class	Glipizide	Tablet	A headache, dizziness, weakness, numbness, pain, skin sensitivity, tremor, blurred vision, insomnia, diarrhea, nausea, constipation.
Biguanides	Metmorphin	Tablet	Trouble breathing, dizziness, nausea, vomiting, slow heart rate, diarrhea, stomach pain,
Dipeptidyl peptidase-4 (dpp-4) inhibitor	Sitagliptin	Tablet	skin/subcutaneous tissue disorders, Nasopharyngitis, Constipation, Peripheral edema, Pharyngitis, Osteoarthritis, URI.
Alpha-glucosidase inhibitor	Acarbose		Flatulence, diarrhea, abdominal pain

Table 6: Summary of key benefits and risks of medication

Medications					
	MET	**DPP4 inhibitor**	**GLP-1 Agonist (Incretin mimetic)**	**SU**	**Glinide**
Risks					
Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild
Gastrointestinal symptoms	Moderate	Neutral	Moderate	Neutral	Neutral
Risk of use with renal insufficiency	Severe	Reduce dosage	Moderate	Moderate	Neutral
Contraindicated in liver failure or predisposition to lactic acidosis	Severe	Neutral	Neutral	Moderate	Moderate
Heart failure / edema	Use with caution in CHF	Neutral	Neutral	Neutral	Neutral
Weight gain	Benefit	Neutral	Benefit	Mild	Mild
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral
Drug-Drug Interactions	Neutral	Neutral	Neutral	Moderate	Moderate

Cardiovascular risk in antidiabetic treatment

Cardiovascular disease is the main leading cause of morbidity and mortality among diabetic patients, the goal of choosing anti-diabetic drugs that do not increase cardiovascular risk but might reduce the risk of cardiovascular diseases and other complications. The recent trials conducted in diabetic patients with heart failure showed a different response to standard medication, with these patients being more prone to develop side effects than patients with the same degree of heart failure but without diabetes. Hence, careful selection of drug therapy paying particular attention to cardiovascular safety is important in optimizing diabetic treatment [16].

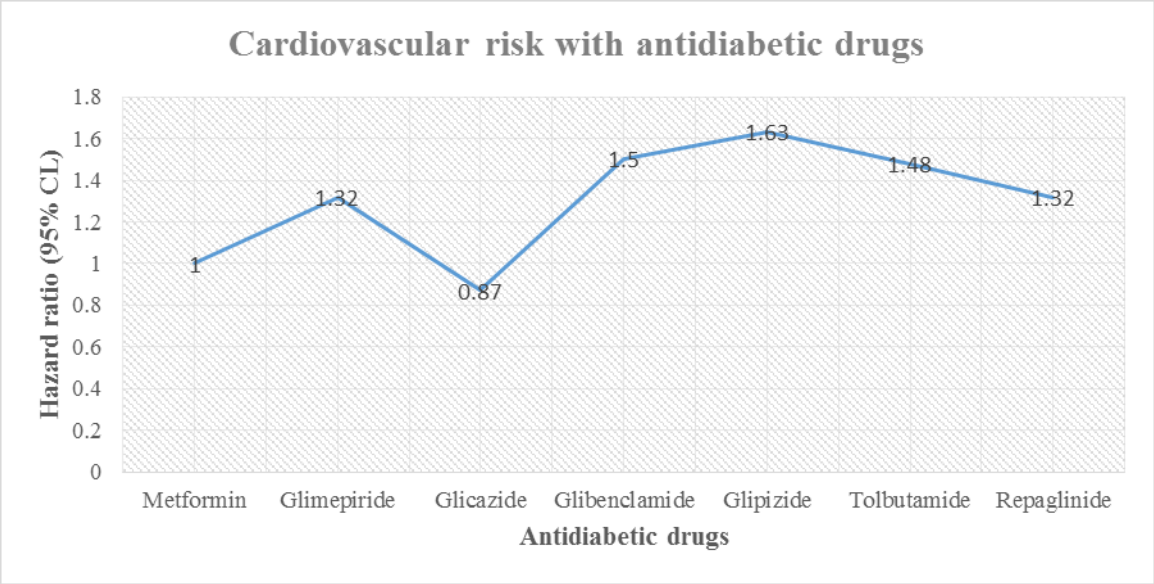

Figure 2: cardiovascular risk with antidiabetic drugs

Survey study

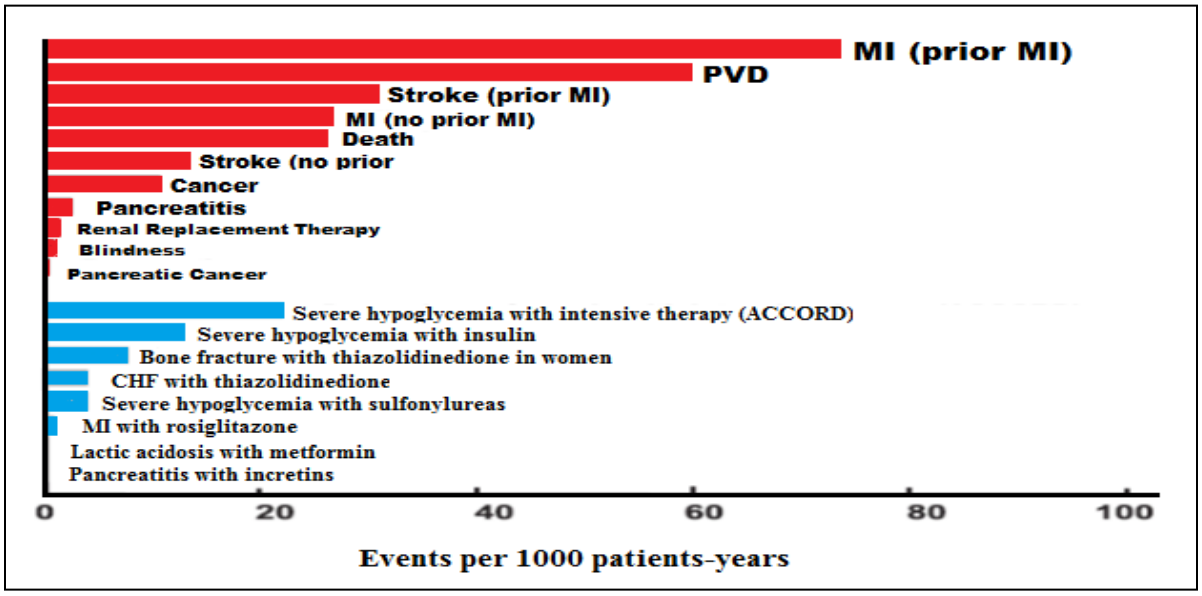

Figure 3: Risk of diabetes complications and adverse events associated with diabetes drug therapies expressed as absolute risk per 1,000 patient-years.

Data were derived from references 13–28. ACCORD, Action to Control Cardiovascular Risk in Diabetes; CHF, congestive heart failure; PVD, peripheral vascular disease; UKPDS, U.K. Prospective Diabetes Study [17].

Banned drug

- Phenformin, an anti-diabetes drug related to metformin, was banned by the amendment G.S.R. No. 780 (E) dt 01-10-2003 (with effect from 01-10-2003) made under Section 26 A of Drugs and Cosmetics Act, 1940 because it caused lactic acidosis, where it increased the pH of the blood.
- The use of rosiglitazone, marketed by drug major GalxoSmithKline as Avandia in many countries, by the amendment G.S.R. No. 910 (E) dt 12-11-2010 (with effect from 12-11-2010) made under Section 26 A of Drugs and Cosmetics Act, 1940.It has reported an increasing evidence of heart risk in studies worldwide. While Europe withdrew the highly controversial drug from its shelves last month, US regulators announced tight curbs on its use
- Expert Committee and in exercise of powers conferred by section 26A of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government hereby prohibits the manufacture for sale, sale and distribution for human use of drug fixed dose combination of Metformin 1000/1000/500/500mg + Pioglitazone 7.5/7.5/7.5/7.5mg + Glimepiride 1/2/1/2mg with immediate effect.

CONCLUSION

Diabetes mellitus is a major healthcare problem in the world. Diabetes mellitus is chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Diabetes mellitus are classified as type I and type II. ADR are any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy. This excludes therapeutic failures, intentional and accidental poisoning and drug abuse. Adverse drug reaction is of type A, B, C, D, E, F and U. Antidiabetic drugs like sulphonylureas, thiazolidinediones, alpha-glucosidase inhibitor, biguanides show major ADR. Thiazolidinediones show CHF, hypoglycemia associated with human insulin analog, hypersensitivity associated with the sulphonylurea, impairment in renal function associated with the biguanides. Clinical trials of antidiabetic drug explain information about safety and efficacy of the drug and it contributes to a better understanding of their possible adverse drug reactions when they are used in the diabetes therapy. Future prospective of my review work is to convey the information regarding the adverse drug reaction of commonly used antidiabetic drug and create awareness about the use of medicines for the effective treatment of diabetes.

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