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A REVIEW ON ADVERSE DRUG REACTIONS OF ANTIDIABETIC DRUGS OF TYPE II DIABETES

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ABSTRACT
Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels. In India, there are estimated 77 million people above the age of 18 years are suffering from diabetes (type 2) and nearly 25 million are prediabetics (at a higher risk of developing diabetes in near future). More than 50% of people are unaware of their diabetic status which leads to health complications if not detected and treated early. Adults with diabetes have a two- to three-fold increased risk of heart attacks and strokes. Combined with reduced blood flow, neuropathy (nerve damage) in the feet increases the chance of foot ulcers, infection, and the eventual need for limb amputation. Diabetic retinopathy is an important cause of blindness and occurs because of long-term accumulated damage to the small blood vessels in the retina. Diabetes is among the leading causes of kidney failure.

KEYWORDS: *Diabetes, Antidiabetic agents, Adverse drug reaction, Adverse drug reaction reporting.*

INTRODUCTION

Type 2 diabetes (T2D) is a condition that happens because of a problem in the way the body regulates and uses sugar as a fuel. That sugar also is called glucose. This long-term condition results in too much sugar circulating in the blood. Eventually, high blood sugar levels can lead to disorders of the circulatory, nervous, and immune systems.

In T2D, there are primarily two problems. The pancreas does not produce enough insulin - a hormone that regulates the movement of sugar into the cells. And cells respond poorly to insulin and take in less sugar.

Type 2 diabetes used to be known as adult-onset diabetes, but both type 1 and type 2 diabetes can begin during childhood and adulthood. Type 2 is more common in older adults. But the increase in the number of children with obesity has led to more cases of type 2 diabetes in younger people.

There's no cure for T2D. Losing weight, eating well and exercising can help manage the disease. If diet and exercise aren't enough to control blood sugar, diabetes medications or insulin therapy may be recommended.

Major clinical features

- Polyuria- The need to urinate frequently.
- Polydipsia-Increased thirst & fluid intake
- Polyphagia-Increased appetite
- Weight loss

Antidiabetic drugs

Antidiabetic drugs are developed to stabilize and control blood glucose levels amongst diabetes patients. Antidiabetic drugs are commonly used to manage diabetes.

Table 1: Antidiabetic drug class.

Drug class	Available formulations (worldwide)	Mechanism	Benefits	Adverse effects and cautions
Biguanides	Metformin	Inhibition of hepatic glucose production and promotion of skeletal muscle glucose uptake	Weight loss or weight neutral Decreased progression from prediabetes to diabetes	Gastrointestinal upset (diarrhea) Lactic acidosis (higher risk with chronic kidney failure) B12 or folate deficiency

Drug class	Available formulations (worldwide)	Mechanism	Benefits	Adverse effects and cautions
			Low cost	
Sulfonylureas and meglitinides	Glipizide Gliclazide Glyburide Glimepiride Nateglinide Repaglinide	Depolarization of the beta cell membrane to increase insulin secretion	Low cost	Hypoglycemia Weight gain Acceleration of loss of beta cell function
Thiazolidinediones	Pioglitazone Rosiglitazone	Activation of nuclear receptor peroxisome proliferator activated receptor gamma (PPAR) to increase adiponectin and improve insulin resistance	Decreased progression from prediabetes to diabetes Redistribution of visceral adipose tissue to subcutaneous	Weight gain (fluid and adipose) Fluid retention Chronic heart failure exacerbation Osteoporosis Bladder cancer Suppressed hematopoiesis
Alpha-glucosidase inhibitors	Acarbose Miglitol Voglibose	Inhibition of hydrolysis of starches and carbohydrates in the gut to decrease absorption	Weight loss (decreased absorption of calories) Decreased progression from prediabetes to diabetes (acarbose, voglibose)	Flatulence Abdominal pain Diarrhea
Glucagon like peptide-1 (GLP-1) receptor agonists	Exenatide (twice daily and weekly) Liraglutide (daily) Lixisenatide (daily) Dulaglutide (weekly) Albiglutide (weekly) Semaglutide (weekly)	Activation of the GLP-1 receptor to augment insulin secretion and inhibit glucagon secretion	Weight loss (decreased meal size) Decreased cardiovascular events (liraglutide, emaglutide)	Nausea Subcutaneous injection Contraindicated for patients with a history of pancreatitis, medullary thyroid carcinoma, or multiple endocrine neoplasia type 2 Possible retinopathy progression (semaglutide)
Dipeptidyl peptidase 4 (DPP4) inhibitors	Sitagliptin Vildagliptin Saxagliptin Linagliptin Gemigliptin Anagliptin Teneligliptin Alogliptin Trelagliptin Omarigliptin Evogliptin Gosogliptin	Inhibition of endogenous GLP-1 inactivation to augment insulin secretion and inhibit glucagon secretion	Weight neutral No cardiovascular harm Oral formulation compared to GLP-1 receptor agonists	Nausea Contraindicated for patients with a history of pancreatitis, medullary thyroid carcinoma, or multiple endocrine neoplasia type 2
Amylin analogue	Pramlintide	Slowing of gastric emptying and inhibition of glucagon secretion	Weight loss (decreased meal size)	Nausea Subcutaneous injection
Sodium-glucose cotransporter 2	Canagliflozin Dapagliflozin	Inhibition of renal glucose resorption	Weight loss (loss of calories in the urine)	Urinary tract infections Genital yeast infections

Drug class	Available formulations (worldwide)	Mechanism	Benefits	Adverse effects and cautions
(SGLT-2) inhibitors	Empagliflozin Ipragliflozin		Decreased cardiovascular events (empagliflozin, canagliflozin)	Normoglycemic diabetic ketoacidosis

Adverse drug reaction

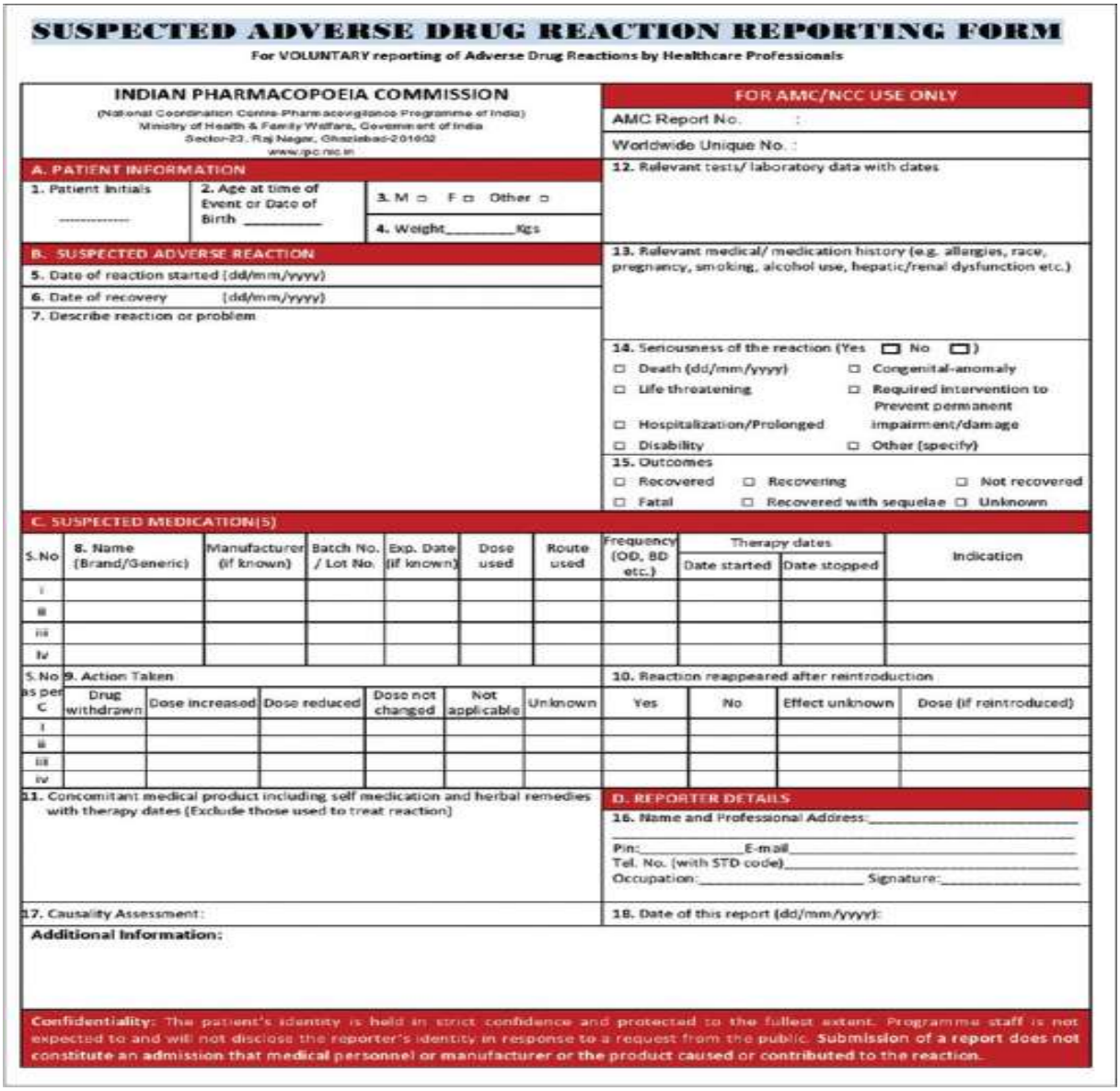
(ADR). Any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This excludes therapeutic failures, intentional and accidental poisoning, and drug abuse. The study of ADRs is the concern of the field known as pharmacovigilance.

Table 2: Classification of adverse drug reaction.

1	Type A (Augmented and predictable)	Relatively commonPharmacologically predictableDose-dependent.Improves if the medicine banned.	Hypoglycemia with sulfonylureasBradycardia with beta blockers, etc.
2	Type B (bizarre or unpredictable)	Involves interaction with a microorganismDose-independentPharmacologically predictable	Dental caries with sugar coated tabletsResistance due to overuse of any one antibiotic, etc.
3	Type C (Chemical)	Related to drug concentrationAn irritant reaction	Extravasation reactionsPhlebitis, etc.
4	Type D (Delivery)	Caused by method of administration or nature of formulationImproves if the medicine is withdrawn or method of delivery changed.	Inflammation or infection around implant particlesInfection at the site of injection, etc.
5	Type E (Exit)	Pharmacologically predictableBegins only when the medicine is stopped or dose is reducedImproves 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 (Hypersensitivity)	Requires activation of immune system Improves if medicine is withdrawn	Anaphylaxis with penicillinallergic 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.



SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION

(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002
www.ipc.nic.in

FOR AMC/NCC USE ONLY

AMC Report No. :

Worldwide Unique No. :

A. PATIENT INFORMATION

1. Patient Initials ----------

2. Age at time of Event or Date of Birth _____

3. M ☐ F ☐ Other ☐

4. Weight_____Kgs

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)

14. Seriousness of the reaction (Yes ☐ No ☐)

☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly

☐ Life threatening ☐ Required intervention to Prevent permanent impairment/damage

☐ Hospitalization/Prolonged ☐ Other (specify)

☐ Disability

15. Outcomes

☐ Recovered ☐ Recovering ☐ Not recovered

☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates		Indication
								Date started	Date stopped	
i										
ii										
iii										
iv										

S.No as per C	9. Action Taken						10. Reaction reappeared after reintroduction			
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

D. REPORTER DETAILS

16. Name and Professional Address:_____

_____

Pin:_____E-mail_____

Tel. No. (with STD code)_____

Occupation:_____ Signature:_____

17. Causality Assessment:

18. Date of this report (dd/mm/yyyy):

Additional Information:

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. **Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.**

Figure 1: ADR reporting and monitoring procedure.

Table 3: Details required for reporting ADR events.

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.

- 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.

Table 4: Antidiabetic drugs and reported ADR.

Thiazolidinedione antidiabetic	Actos	Tablet	Upper respiratory tract infection, headache, sinusitis, Myalgia, Tooth disorder, pharyngitis
Human insulin analogue	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 5: Summary of key benefits and risks of medication.

Neutral	Neutral	Neutral	Moderate	Mild
Moderate	Neutral	Moderate	Neutral	Neutral
Severe	Reduce dosage	Moderate	Moderate	Neutral
Severe	Neutral	Neutral	Moderate	Moderate
Use with caution in CHF	Neutral	Neutral	Neutral	Neutral
Benefit	Neutral	Benefit	Mild	Mild
Neutral	Neutral	Neutral	Neutral	Neutral
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.

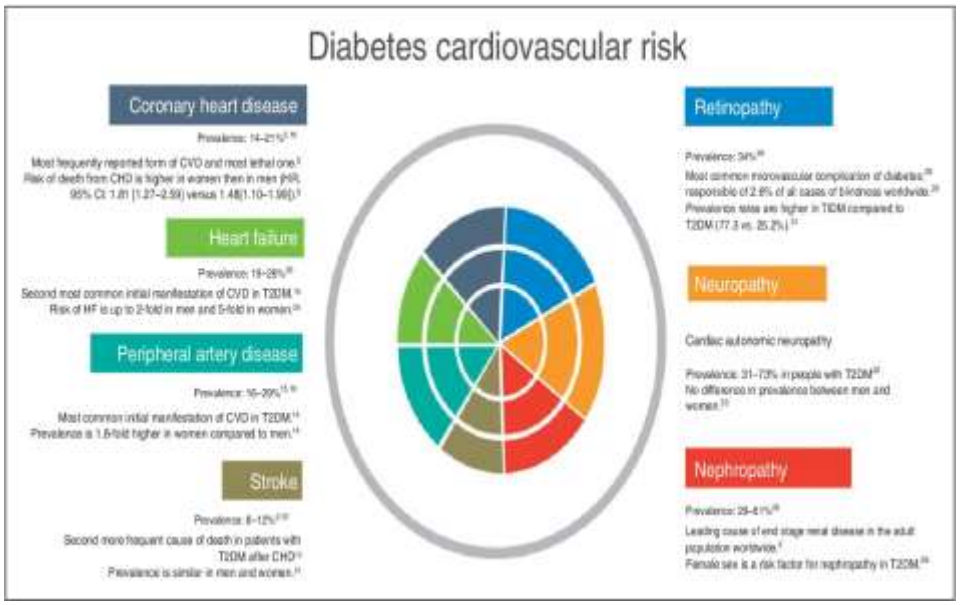


Figure 2: cardiovascular risk with antidiabetic drugs Survey study.

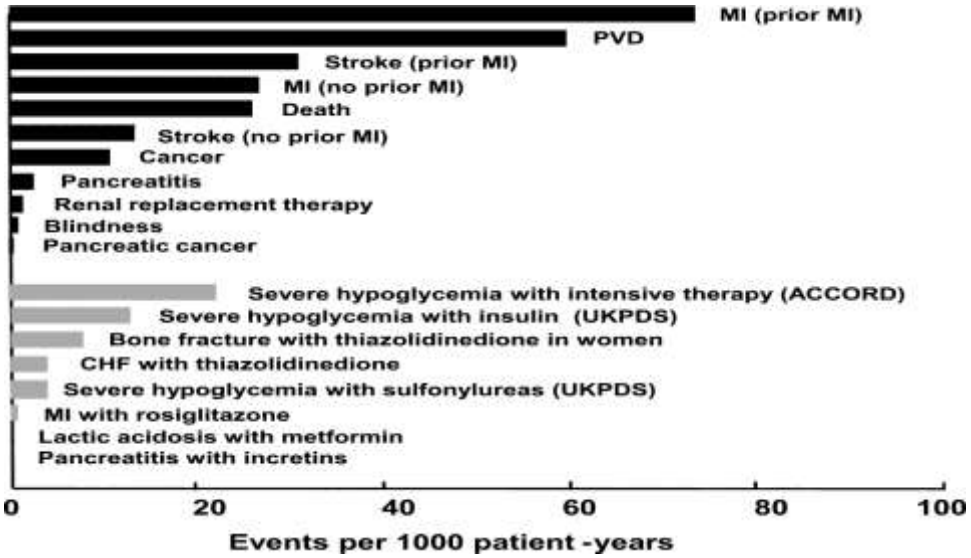


Figure 3: Risk of diabetes complications and adverse events associated with diabetes drug therapies expressed as absolute risk per 1,000 patient-years.

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.

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 GlaxoSmithKline 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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