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## UNCOMMON SIDE EFFECTS OF COMMONLY USED ANTI-DIABETICS: TIME TO MONITOR THEM

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**ABSTRACT:** Diabetes, a chronic endocrine metabolic disorder, is managed using several anti-diabetic medications. Being a chronic disease requiring lifelong medications, the long-term safety profile and patient acceptance are crucial to achieving therapeutic success. The available medications are known to have common side effects such as hypoglycemia, weight gain, and gastrointestinal adverse effects. Uncommon adverse effects, although rare can be troublesome in some patients and may lead to decreased medication adherence/concordance and hence treatment failure. There are reports of metformin being associated with lactic acidosis and sulfonylureas with cholestatic jaundice. Pioglitazone can have a rare adverse effect of pulmonary edema with or without congestive heart failure. Acarbose can be the reason for ileus and sub ileus in patients. Glucagon-like peptide-1 receptor agonists like liraglutide can cause pancreatitis. Careful consideration of anti-diabetics while prescribing, adequate clinical and laboratory monitoring and proper counseling of patients might help in prevention and early detection of these rare but severe adverse effects of anti-diabetics.

**INTRODUCTION: Background:** Diabetes, a chronic endocrine metabolic disorder, is a global health concern. The World Health Organization (WHO) reports that around 9% of adults have diabetes <sup>1</sup>. The global prevalence of diabetes is estimated to increase to around 366 million by the year 2030.<sup>2</sup> Though the available medications are efficacious in lowering high blood, they are not devoid of adverse effects. It is the responsibility of healthcare providers to ensure that patients receive safe and effective medications.

To achieve this goal, it is crucial to screen and monitor adverse drug reactions (ADR). WHO defines an adverse drug reaction as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function' <sup>3</sup>.

Although many of the common side effects of anti-diabetic medications are reported, the rare one softens go unnoticed and unreported because of lesser knowledge about these ADRs among healthcare practitioners. Council for International Organizations of Medical Sciences (CIOMS) defines a rare ADR as one whose occurrence is greater than or equal to 1/10000 and less than 1/100 and very rare ADRs as those with an occurrence of lesser than 1/10000.<sup>4</sup>

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The purpose of this review is to highlight the rare adverse drug reactions of commonly used anti-diabetic medications.

**Search Criteria:** The search criteria of this review included manual search of textbooks available in the Institutional Library, Google Scholar, PubMed and Micromedex electronic database latest version (Micromedex® 2.0, electronic version) The search terminologies included ‘rare side effects’, ‘anti-diabetic’, ‘diabetes medications’ and ‘uncommon side effects’.

**Common Adverse Drug Reactions to Anti-diabetics:** <sup>5, 6</sup> Hypoglycemia is associated with almost all the available anti-diabetic drugs, reasons being inappropriate dosage, improper counseling about the disease, drug, and dietary parameters. Insulin administration is commonly associated with injection site reactions, including erythema, edema,

and pruritus. Metformin is associated with common adverse effects like diarrhea, flatulence, indigestion, malabsorption syndrome, nausea, vomiting, headache, and cobalamin deficiency. Glimepiride and glipizide are associated with adverse effects like dizziness, syncope, headache, and nausea, and increased serum levels of liver enzymes. Pioglitazone is known to produce adverse effects like edema, hypoglycemia, upper respiratory tract infection, heart failure, headache, fractures, myalgia, sinusitis, and pharyngitis. Acarbose is mainly associated with gastrointestinal adverse effects like diarrhea, flatulence and abdominal pain. Saxagliptin and sitagliptin is associated with peripheral edema, headache, and abdominal pain.

**Rare Adverse Effects:** The rare adverse effects associated with commonly used anti-diabetics are mentioned below in **Table 1**.

**TABLE 1: UNCOMMON SIDE EFFECTS OF ANTIDIABETICS**

Anti-diabetic	System affected	Rare and very rare adverse drug reactions
Metformin <sup>5, 6, 8, 9, 10, 11</sup>	Metabolic	Lactic acidosis (Rare; 0.03 cases per 1000 patient years, with 0.015 fatal cases per 1000 patient years)
Glimeperide <sup>5, 6</sup>	Hepatobiliary	Hepatitis
	GI	Epigastric fullness
	Cardiovascular	Angioedema, hypotension, shock
	Hematopoietic	Agranulocytosis, aplastic anemia, disulfiram-like reaction, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia
	Immune	Anaphylaxis, hypersensitivity
	Dermatological	Maculopapular rash, morbilliform rash, skin photosensitivity, Stevens-Johnson syndrome
	Metabolic	Weight gain, hyponatremia, syndrome of inappropriate antidiuretic hormone (SIADH)
	Hepatobiliary	Abnormal hepatic function tests, cholestatic jaundice, hepatic failure, hepatic porphyria, hepatitis
	Miscellaneous	Accommodation disturbance (early during treatment), anorexia
	GI	Blood in stool
Glibenclamide/ Glyburide <sup>5, 6, 12, 13, 14, 15, 16</sup>	CNS	Gait instability, migraine, vertigo
	Cardiovascular	Arrhythmia, disulfiram-like reaction, edema, hypertension
	Hematopoietic	Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, pancytopenia, porphyria, thrombocytopenia
	Dermatological	Photosensitivity
	Metabolic	Hyponatremia, SIADH
Pioglitazone <sup>5, 6, 17</sup>	Hepatobiliary	Cholestatic jaundice syndrome (rare), Hepatitis (rare) jaundice, liver injury
	Miscellaneous	A decrease in platelet aggregation and subsequent increase in coagulation time, anorexia, conjunctivitis, hypertonia, retinal hemorrhage
	Cardiovascular	Pulmonary edema and/or congestive heart failure, dyspnea (associated with weight gain and/or edema)
	Hepatobiliary	Hepatic failure (very rare), hepatitis, increased transaminases
	Miscellaneous	Bladder cancer, blurred vision, increased creatinine phosphor kinase, macular edema (new onset or worsening), rhabdomyolysis, decreased visual acuity
Acarbose <sup>5, 6, 18, 19</sup>	GI	Ileus and subileus, lymphocytic colitis
	Hematopoietic	Thrombocytopenia
	Dermatological	Erythema, exanthema, rash, urticaria
Sitagliptin <sup>5, 6</sup>	Hepatobiliary	Hepatitis, jaundice, liver damage
	GI	Gastritis ( <i>Helicobacter pylori</i> ), gastroesophageal reflux disease
	CNS	Depression, migraine

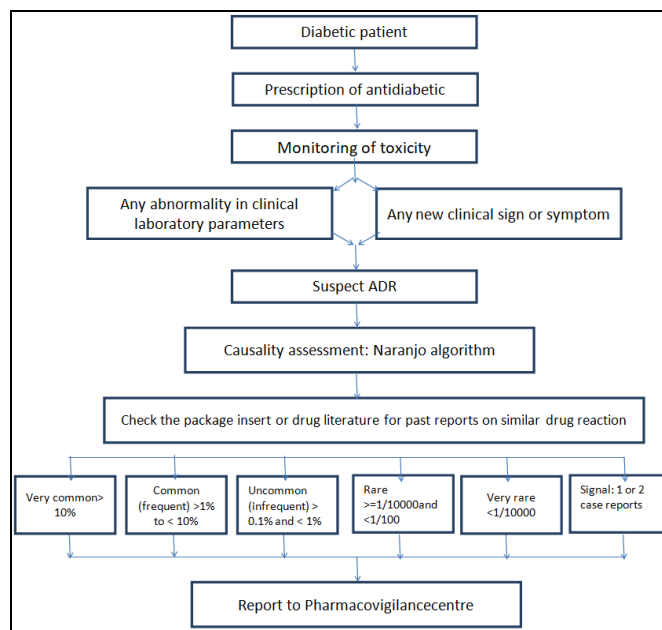
	Cardiovascular	Angioedema, bundle branch block, hypertension, hypotension, orthostatic hypotension
	Hematopoietic	Anemia
	Immune	Anaphylaxis, hypersensitivity, hypersensitivity vasculitis
	Dermatological	Acne rosacea, exfoliative dermatitis, Stevens-Johnson syndrome
	Hepatobiliary	Increased liver enzymes, liver steatosis
	Miscellaneous	Acute renal failure, erectile dysfunction, peripheral neuropathy, renal insufficiency, severe arthralgia
Saxagliptin <sup>5</sup>	Cardiovascular	Angioedema
	Immune	Anaphylaxis, immune thrombocytopenia
	Dermatological	Exfoliative dermatitis, skin rash
	Hepatobiliary	Acute pancreatitis
	Miscellaneous	Increased creatine phosphokinase, increased serum creatinine, severe arthralgia
Exenatide <sup>20</sup>	Hepatobiliary	Acute Pancreatitis
Liraglutide <sup>21</sup>	Hepatobiliary	Acute and Chronic pancreatitis
Canagliflozin & Dapagliflozin <sup>22</sup>	Renal	Acute kidney injury

**Early Detection:** Knowledge about rare adverse drug reactions and active reporting of suspected adverse drug reactions by healthcare professionals is necessary for early detection and prevention of possible drug-related problems. Sometimes a new adverse event, which is not reported earlier, may be seen in patients treated with medicines. These are called signals. A signal refers to “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”. Usually, rare ADRs and signals are best documented by spontaneous reporting by healthcare professionals. ADRs can also be detected by encouraging patients to voluntarily report any occurrence of unusual symptoms. In addition, medication chart review and progress notes, computerized surveillance, direct observation by physicians and other healthcare providers can also facilitate ADR detections.<sup>20</sup> Adequate knowledge about the above mentioned ADRs among healthcare professionals can be helpful in early detection using these strategies. A systematic reporting of ADRs either by trained professionals or pharmaceutical companies through post-marketing surveillance are other methods for detection<sup>21</sup>.

**Prevention Strategies:** ADRs can be categorized as preventable and not preventable<sup>22</sup>. ADRs which cannot be prevented should be carefully monitored for their early detection and management. There are strategies to avoid preventable ADRs. Medication errors such as inappropriate dose, indication, presence of contraindication for use of the drug; hepatic or renal impairment; and improper administration technique are a few factors which

may lead to ADRs and should be properly reviewed in each patient. All unnecessary drugs with no indication or therapeutic duplication must be removed from the patient chart. Always suspect drugs as a precipitating factor for any new symptoms. Carry out a causality assessment as far as possible. Proper education of the patients regarding their medications is also a good tool to prevent ADRs<sup>23</sup>.

**An Approach for Detection of Rare ADRs:** Fig. 1 shows an approach for early detection and monitoring of rare side effects.



**FIG. 1: APPROACH FOR DETECTION OF RARE ADRS**

**CONCLUSION:** Uncommon side effects, although rare can become bothersome for patients and may lead to decreased medication adherence and hence treatment failure. Careful consideration

of the ADRs of anti-diabetics while prescribing, carrying out adequate clinical and laboratory monitoring and proper counseling of patients might help in prevention and early detection of these rare but severe side effects of anti-diabetics.

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