A Review on Drug-Drug and Drug-Food Interactions in Patients During the Treatment of Diabetes Mellitus

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ABSTRACT

Drug interaction is defined as the modification of the effects of a drug (object drug) by the prior and/or the concomitant administration of another drug (precipitant drug). Drug interaction may either increase or decrease the intended effect of one or both drugs. It may transform the diagnostic, preventive or therapeutic activity of any drug. Drug-interactions can be an extremely main contributory factor for the incidence and occurrence of adverse drug reactions and adverse drug events. The rate of occurrence and incidence of drug interactions is much higher in patients receiving combinations of drugs or poly-pharmacy or suffered from co-morbidity of diseases such as diabetes, hypertension, peptic ulcer, fungal infections and neurodegenerative disorders, which require prolong and multi treatments and the risk of drug interaction will increase as they are treated with multi-therapies. It is concluded that diabetic patients are at higher risk for drug interaction as receiving a combination of therapies for diabetic complications as well, so that the rate of occurrence of drug interaction is rapidly amplifying. Diabetes mellitus has been considered as a foremost public health challenge around the world because of its high prevalence and associated increase in morbidity and mortality. The main objective of this review study is to highlights the various drug interactions likely drug-drug and drug-food interactions as well as reports unwanted effects of other treatment associated with antidiabetic agents in the diabetic patients.

Key words: Drug interaction, Adverse drug reactions, Polypharmacy, Diabetes Mellitus, Drug-drug interaction, Drug-food interaction.

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INTRODUCTION

An interaction is said to arise when the effects of one drug is altered by the existence of an additional drug(s), food/drink and/or an environmental essentials at the same time as a therapeutic combination could lead to an unpredicted alteration in the form of the patient, this would be illustrated as an interaction of potential clinical implication.[1,2] Drug interactions described an important and extensively under acknowledged source of the prescription errors. Final outcome of any combination may be synergism or additive effect of one and/or more drugs, the antagonism or harmful effect of one or more drugs moreover the alteration of effect of one or more drugs and/or the production of idiosyncratic effects. Drug interaction (DI) is defined as the modification of the effects of a drug (object drug) by the prior and/or concomitant administration of another drug (precipitant drug). Drug interaction may either increase or

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decrease the intended effect of one or both drugs. It may transform the diagnostic, preventive or therapeutic activity of any drug.[2] In polypharmacy, it is so important to find out the prevalence and rate of occurrence of drug interactions furthermore serious implications in hospitalized patients. As well, it is more significant to observe and detect agents that are the majority to produce unsafe and harmful interactions.[3] As per the survey, the frequency and incidence of drug-drug interaction ranges from 3 to 5% in the patients taking a few drugs while it is around 20% in patients receiving many drugs.[4,5] DIs can take place in numerous ways; such as pharmacodynamic interaction, in which receptor effects of diverse agents interacts to produce synergy or the antagonism of the drug action/outcome.

DIs can be an extremely main contributory factor for the incidence and occurrence of adverse drug reactions (ADRs) and adverse drug events.[5] The incidence and rate of occurrence of drug interactions is much higher in patients receiving combinations of drugs or poly-pharmacy or suffered from co-morbidity of diseases such as diabetes, hypertension, peptic ulcer, fungal infections and neurodegenerative disorders, which require prolong and multi treatments and the risk of drug interaction will increase as they are treated with multi-therapies.[6] Diabetic patients often comprise a number of coexisting health problems likely dyslipidemia, hypertension, etc. In addition to oral Antidiabetic drugs or insulin, they may need other drugs to control the coexisting problems such as statins for treatment of high cholesterol level; fibrates for treating high triglycerides level; ACEIs or ARBs for treatment of high blood pressure, heart, or kidney failure state; diuretics, CCBs or beta-blockers for high blood pressure and aspirin or clopidogrel to prevent heart attack.[5] It is concluded that diabetic patients are at higher risk for drug interaction as receiving a combination of therapies for diabetic complications as well, so that the rate of occurrence of drug interaction is rapidly increases.

Diabetes Mellitus (DM) is a major chronic life threatening disorder, characterized by the homeostasis of carbohydrate and lipid metabolism is improperly regulated by the insulin (pancreatic hormone), resulting in an increased level of blood glucose. Currently, DM represents one of the main threats to human health.[7] DM is a serious metabolic disease that has a significant impact on the quality of life, healthiness and life expectancy of the patients, as well as on the health care system.[8,9] DM is a chronic disorder characterized by impaired metabolism of glucose and lipids due to defect in insulin secretion (beta cell dysfunction) and/or insulin action (insulin resistance).[9] Diabetes has been regarded as a major public health challenge around the world because of its high prevalence and associated increase in morbidity and mortality. As the condition of hyperglycemia progresses, increases in tissue or vascular damage may lead to obesity, hypertension, advancing age, accumulation of harmful agents in the vascular endothelium causing development of microvascular complications.[10]

International Diabetes Federation reports that diabetes affects about 382 million people world-widely and it is estimated that this number will rise to 592 million by 2035.[11] DM is now the leading cause of many serious complications such as cardiovascular, renal and other serious comorbidities.[12] The distinctive properties of DM are chronic hyperglycemia, microvascular (eg. retinopathy, nephropathy and neuropathy) as well as the macrovascular (eg. coronary artery disease (CAD), hypertension (HT), atherosclerosis and stroke) pathologies with more than 17.5 million deaths globally which furthermore attributable to cardiovascular complications.[13] Diabetes is undoubtedly one of the most challenging health problems in the 21st century.[14]

Although numerous interactions affecting hypoglycemic but few are of major significance (Table 1). These agents can be used moderately in safety with almost all other medications with a couple notable exceptions:

Interaction of antifungal agents with antidiabetic agents: Epidemiological studies report that numerous patients suffering from diabetes are also prone to fungal infections.[4,15] In such antifungals agent such as fluconazole, itraconazole, miconazole, ketoconazole etc and thiazolidinedione (antidiabetic agents) such as pioglitazone or rosiglitazone are administered concomitantly. Itraconazole is well-known to inhibit Cytochrome P-450 enzyme system; hence there is a possibility of occurrence of pharmacokinetic type of drug interactions with concomitantly used drug(s). Erythromycin derivatives and antifungal agents are the strong inhibitors of CYP3A4 such as azole; which may also enhance the hypoglycemic effect of rapaglinide.[16,17] Janadri *et al.* concluded that, throughout simultaneous treatment of the diabetes mellitus with fungal infections and the therapeutic dose of thiazolidinediones and itraconazole do interact.[4,15] Therefore it is necessary to adopt therapeutic drug monitoring (TDM) so as to readjust dose and frequency of administration of these drugs, which are employing concomitantly to avoid the patients from severe hypoglycemia.

Interaction of antihypertensive agents with antidiabetic agents: In the diabetic patients hypertension is one of the major and common health problems which are often

complicated to treat and results considerable morbidity and mortality.[5] Diabetic people showed higher incidence of hypertension which is probably 1.5-2.0 times more than in the general people. Beta blockers such as propranolol are frequently used as first line therapy in patients with hypertension including those with diabetes mellitus. A potent second generation sulfonylureas (antidiabetic drug) such as glipizide, furthermore which causes stimulation of beta cells of the islet of langerhans of pancreas to booster the secretion of insulin and reducing blood glucose. [5] Potential mechanisms by which beta blockers may contribute to the development of diabetes comprises weight gain and adaptation of the beta-receptor mediated insulin secretion from the pancreatic β-cells. When access to beta-adrenergic receptor sites is blocked by the propranolol, then the inotropic, chronotropic and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. The rise in plasma adrenaline and other counter-regulatory hormones during hypoglycemia; enhanced by the blockade of beta adrenoceptor.[15,18]

Sen *et al.* showed that on repeated administration of propranolol contributes to significantly increase the hypoglycemic activity of glipizide in diabetic animals. While in diabetic animals repeated administration of propranolol followed by glipizide potentiated the hypoglycemic activity. They also suggests that during simultaneous treatment of the co-morbidity of hypertension and diabetes with propranolol and glipizide, the frequency of administration and dosage of glipizide are to be readjusted accordingly in order to avoid severe hypoglycemia.[5] It is concluded that there is a need to readjust the dose and frequency of antihypertensive drugs when taken along with antidiabetics; so that to avoid the patients from severe hypoglycemia.

Interaction of antipsychotics with antidiabetic drugs: Psychiatric treatment of diabetic patients is focused on the treatment of anxiety and depression with the administration to diabetes and on the improvement in quality of life with disease. Antidepressant drugs are most commonly administered psychiatric medication. They are used for the anxiety and depression, also used for the treatment of painful diabetic neuropathy. As Lustman *et al.* shown that the glycosylated hemoglobin reduces throughout the open treatment phase and remains significantly reduced during depression-free maintenance, regardless of the fact whether the patients are treated by an antidepressant, sertraline in this case, or by placebo.[19] Another study with sertraline demonstrated that a specific minor population of diabetics with low financial income showed a significant reduction in glycosylated hemoglobin after the initiation of pharmacologic treatment of depression in comparison with placebo.[20]

It is accomplished that the blood glucose, body weight, blood pressure, and renal functions influences when a diabetic patient treating with antidepressants; moreover it influences glycemia, so it is necessary to advise the patient ahead that a dosage change in insulin or oral antidiabetic drugs may be necessary. The body weight increases the most after tricyclic antidepressants (TCA) and mirtazapine use and the least after Selective serotonin reuptake inhibitors (SSRI), Monoamine Oxidase Inhibitors (MAOI) a trazodone. An increase in blood glucose was described in association with TCA, a decrease after SSRI and MAOI.[21] The longest used TCA decrease insulin secretion, increase blood glucose, appetite for the sweets and body weight. TCA such as Amitriptyline is used even for treatment of diabetic painful peripheral neuropathy. SSRI decrease blood glucose (even 30% decrease in fasting glycemia has been illustrated), temporarily reduce body weight (most often illustrated in fluoxetine), however, they increase body weight on long-term use. Cytochrome 3A4 enzyme (CYP 3A4) inhibition by fluvoxamine may interrupt with the metabolism of oral antidiabetic drugs. While CYP 2C9 inhibition by fluoxetine, fluvoxamine or sertraline can interfere with the metabolism of antidiabetics such as sulfonylurea and tolbutamide. In combination they can lead to hypoglycemic condition, as these antidepressants because an increase in the level of the antidiabetic drugs (sulfonylurea and tolbutamide).[21] MAOI such as moclobemide reduces the blood glucose and can thus lead to the hypoglycemic conditions. On the other hand, it usually does not increase body weight. Norepinephrine dopamine reuptake inhibitor (NDRI) such as bupropion is neutral regarding the influence on body weight. Higher doses in combination with insulin lower seizure threshold (the risk of epilepsy is increased especially in patients with concomitant mental anorexia). Bupropion attenuates sexual dysfunction and facilitates smoking cessation. Both effects are of great importance in diabetic patients, as they suffer from diabetes-associated sexual dysfunction and have elevated cardiovascular risk from smoking. [21] Noradrenergic and specific serotonergic antagonist (NaSSA) mirtazapine increases appetite and body weight, which is undesirable in diabetic patients. Furthermore, it can lead to an increase in glycosylated hemoglobin and thus deteriorate a long-term glycemic control.

Interaction of Phenylbutazone with antidiabetic drugs: Phenylbutazone can cause severe hypoglycemia when given together with oral sulfonylureas, due to displacement of these agents from plasma protein binding sites and

inhibition of their metabolic clearance. The hypoglycemic effects of tolbutamide affected the most. Phenylbutazone should be avoided and an alternate NSAID can be used.[22] Phenylbutazone should be avoided and contraindicated during the treatment of diabetes because the administration of oral hypoglycemic agents along with this drug may leads to severe hypoglycemia.

Interaction of Alcohol with antidiabetic drugs: Alcohol can cause a disulfiram-like reaction when taken in combination with oral sulfonylureas, particularly chlorpropamide. Persons experience flushing, sensations of warmth, dizziness, nausea and tachycardia. Alcohol is best avoided since the amount consumed does not necessarily correlate with occurrence or severity of the reaction. Diabetics not prescribed sulfonylureas are also wise to abstain or limit alcohol consumption as it has adverse effects on glycemic control with a tendency towards hypoglycemia. Pre-existing hypoglycemia can be potentiated. Acute and chronic alcohol consumption can also affect metabolic clearance of some hypoglycemics, further contributing to loss of glycemic control.[16,22] So that the use of alcohol should be contraindicated and avoided during the treatment of diabetes, to prevent the severe hypoglycemia.

Interaction of Antihyperlipidemics with antidiabetic agents: Fibrate antihyperlipidemics and some beta blockers can displace sulfonylureas and repaglinide from plasma protein binding thereby potentiating their effects and possibly causing hypoglycemia. Whereas Cholestyramine increases the hypoglycemic effect of acarbose and Nicotinic acid worsens glycemic control and possibly increases insulin resistance.[22] So that the use of these drugs should be avoided and contraindicated during the treatment of diabetes because the administration of oral hypoglycemic agents along with these drugs may leads to severe hypoglycemia.

Miscellaneous drug-drug interaction associated with Antidiabetic drugs: After diagnosed with diabetes, a large number of medications required as appropriate therapy. These include medications for dyslipidemia, hypertension, antiplatelet therapy, and glycemic control.

Table 1: Unwanted effects of various drugs with antidiabetic agents

Drug or Class of drug	Unwanted effects of drugs with antidiabetic agents in diabetic patients	References
Amitriptyline	Increase glycemia, Increase body weight.	[21]
SSRI (Citalopram, sertraline)	Reduce glycemia. Increase body weight.	[19]
MAOI (moclobemide)	Reduce glycemia. Do not increase body weight.	[21]
SNRI (Venalafaxine, duloxetine)	Duloxetine increases fasting glycemia, Do not increase body weight.	[21]
NaSSA (mitrazapine)	Increase body weight and glycosylated hemoglobin.	[21]
St. John's wort (hypericin)	Do not increase body weight, risk of drug interactions.	[21]
Itraconazole (antifungal)	Produces hypoglycemic effect when administered with Thiazolidinediones.	[4,]
Propranolol (Beta blocker)	Produces hypoglycemic effect with glipizide.	[5]
Phenylbutazone	Severe hypoglycemia with oral sulfonylureas.	[22]
Alcohol	Potentiate pre-existing hypoglycemia, acute and chronic alcohol consumption contributing to loss of Glycemic control.	[16, 22]
Fibrates (antihyperlipidemics)	Cause hypoglycemia; also potentiate hypoglycemia by displacing sulfonylureas and rapaglinide from plasma protein binding.	[22]
Gemifibrozil	When administered with rapaglinide, enhances the activity of rapaglinide which may cause hypoglycemia.	[28]
Indomethacin	Increase insulin secretion from pancreas, decrease gluconeogenesis, insulin clearance and increase in glucose uptake in periphery.	[27]
Rifampicin, Phenobarbital	They decreases the hypoglycemic activity when admisinstered with sulfonylureas, meglitinides and thiozolidinediones.	[28, 34]
Co-trimoxazole	Coadministration of co-trimoxazole with sulfonylureas increases the risk of hypoglycemia.	[46]
Cimetidine	Cimetidine may compete with Metformin for renal elimination, which enhances the Metformin level; it may result in hypoglycemia and Metformin associated lactic acidosis.	[47, 48]

So many medications can be overwhelming, and it is imperative that patients are thoroughly educated about their drug regimen.[8,23] Patients have many concerns when multiple medications are started, including prescribing errors, the cost of medications, and possible adverse effects. Significantly, 58% of patients worry that they will be given medications that have drug interactions that will adversely affect their health.[24,25] The drug should not be prescribed in patients with moderate or severe renal impairment or in patients at risk for developing volume depletion.[26,29] The administration of oral hypoglycemic agents should be adjusted and manipulated along with these drugs; either it may leads to severe hypoglycemia.

DRUG-FOOD INTERACTIONS

According to the World Health Organization (WHO) reports, increased in daily fruit and vegetable intake could be beneficial to prevent the major chronic non-communicable diseases. It has been reported that low fruit and vegetable intake is among the top-10 risk factors contributing to mortality.[30] Increase in fruit and vegetable intake can also help to displace food high in saturated fats, sugar or salt. Observed drug-phytochemical interactions, additionally to interactions with dietary micronutrients indicate various possibilities for improved therapeutic strategies. However, several reports have observed the effects of herbal medicines and plant foods on drug bioavailability. It has been suggesting that important food and phytochemical modulation of drug transporters and drug-metabolizing enzymes leading to potential important nutrient-drug interactions.[30] Drug-Food interactions can result in two main clinical effects; decreased in bioavailability of a drug resulted in treatment failure or an increased in bioavailability, moreover increases the risk of adverse events and may even precipitate toxicities. Drug metabolizing enzymes and drug transporters play vital roles in the alteration of ADME (drug absorption, distribution, metabolism, and elimination). Acting alone or in combination with each other, they can affect and alter the pharmacokinetics and pharmacodynamics of a drug. Interaction between the drug metabolizing enzymes and transporters is one of confounding aspect that has been recently shown to contributable for potential multifaceted drug interactions.[31] Drug-food interaction shown that the selection or choice of drug in diabetic patients may be affected by the presence of food, so that therapeutic efficacy of any drug may alter because of the drug-food interaction which furthermore harmful to the patient health.

***Syzygium Cumini* (Jamun):** Syzygium Cumini or Jamun (Hindi), Jamun fruit also called as sIndian blackberry. Syzygium cumini (Family-Myrtaceae) at a dose level of 50 mg/kg also showed significant decrease in blood glucose level. Also, it has shown significant decrease in blood glucose levels of alloxan-induced diabetic rats. *S. cumini* act on glucose transporter (GLUT-4), PPAR gamma and PI3K involved in glucose transport. Activity suggests that *S. cumini* activate glucose transport in a PI3K-dependent manner. Shweta and her colleagues reported that oral administration of ethyl acetate and methanol extracts of Syzygium cumini (200 and 400 mg/kg) showed significant decrease in blood glucose level.[32] It has been reported that different solvent extracts extracted sequentially were analyzed for glucose uptake activity at each step, methanol extracts were found to be significantly active at 100 ng/ml dose comparable with insulin and Rosiglitazone.[33,34] Jamun traditionally used as antidiabetic agent; so that it should be avoided and contraindicated during the treatment of diabetes because the administration of oral hypoglycemic agents along with Jamun may leads to severe hypoglycemia.

***Momordica Charantia* (Karela):** Bitter Melon or *Momordica Charantia*, also known as Karela or Balsam pear; is a Tropical vegetable and common food in Indian cusine and has been used extensively in folk medicine as a remedy for diabetes.[35] The fruit of *Momordica Charantia* is considered as tonic, stomachic, stimulant, emetic and laxative. Also the fruit is useful in treatment of gout, rheumatism and sub-acute cases of the spleen and liver diseases as well it is supposed to purify blood and dissipate melancholia. It has also been shown to have hypoglycemic properties in the animal as well as effective in human studies.[36] It has been reports that *Momordica Charantia* intake increases the number of beta cells in the pancreas thereby improving the body's ability to produce insulin. The fruit has also shown the ability to promote insulin release by enhancing cells uptake of glucose and potentiate the effect of insulin.

Oral administration of fresh fruit juice (dose, 6 c.c./kg) decreases the blood glucose level in normal and alloxan-induced diabetic rabbits. Bitter melon's hypoglycemic effects have been shown in animal and human studies. P-insulin, a polypeptide from the fruits and seeds, results in rapidly decreased and stabilized the blood glucose level in rats. It improves blood glucose levels by increasing glucose uptake and glycogen synthesis in the liver, muscles, and fat cells as well as it improve the insulin release from pancreatic beta cells and repair or promote new growth of insulin-secreting beta cells.[35] A recent scientific study at JIPMER, India has found and proved that bitter melon enhances the insulin sensitivity. Also, the Philippine Department

of Health in 2007 concerned a circular stating that bitter melon is a scientifically authorized herbal medicinal plant which can reduce the elevated blood glucose levels. This study exposed that a 100 mg/kg/day (milligram per kilo dose per day) is comparable to 2.5 mg of well-known antidiabetic drug Glibenclamide which taken twice per day. Oral administration of 50-60 ml of the bitter melon juice has shown good results in the clinical trials.[35,36]

Extremely high doses of the juice (bitter melon) can cause diarrhea and abdominal pain. Bitter melon should not be used and avoided for small children or anyone with hypoglycemia, as it may trigger or worsen low blood glucose or hypoglycemia. The use of *Momordica Charantia* should be avoided in pregnant women as it stimulates the uterus and may cause premature birth. Administration of bitter melon may potentiate the action of insulin; produces synergistic effects with antidiabetic drugs and also may potentiate the cholesterol-lowering drugs. Moreover, the diabetic patients taking/receiving hypoglycemic drugs (likely Phenformin and chlorpropamide) or insulin,[35] the use of bitter melon should be avoided or taken with caution as it may potentiate the effectiveness of the drugs and may leading to severe hypoglycemia.

Garlic (*Allium sativum*): Garlic has been widely used for reducing the high cholesterol. Garlic has also been used for treating or myriad other disorders (such as atherosclerosis, diabetes, fungal infections, cancer, hypertension, myocardial infarction and peripheral vascular disease) with little scientific evidence supporting its benefits. Jain and Vyas had shown the hypoglycemic effect of garlic extracts with water or several other different organic solvents on the oral glucose tolerance in both normal and alloxan-induced diabetic rabbits.[37] Garlic oil shown hypoglycemic effect in diabetic animals as well as in humans has also been reported.[38-40] Co-administered of glimepiride with garlic resulted in tight glycemic control due to the hypoglycemic properties of garlic as well as glimepiride.[41] Sheela and Augusti reported that sulfur containing amino acid S-allyl cysteine sulfoxide (alliin) in garlic has more potential to control the diabetic condition in rat as compared to insulin and Glibenclamide.[42] Eldi *et al*. reported that oral administrations of the garlic extract had shown significant decrease in the levels of serum glucose, triglycerides and total cholesterol levels while shown increase in serum insulin levels in diabetic rats. It was reported that the antidiabetic effect of the garlic extract was more effective than that observed with Glibenclamide administration (600 microg/kg).[43] *Allium sativum* results in hypoglycemia when taken with chlorpropamide. Patients taking diabetes medications should be cautioned because of the possibility of hypoglycemia.[43] The use of garlic should be avoided or taken with caution as it may potentiate the effectiveness of the drugs and may lead to severe hypoglycemia.

PATIENTS RECEIVING DIABETES MEDICATIONS

Glucose control in both insulin-dependent or type 1 diabetes mellitus (T1DM) and non-insulin dependent (or T2DM) diabetics can be affected by the consumption of hypoglycemic herbs.[24,25] More than 400 plants have been traditionally used for their hypoglycemic action; of these, Aloe vera, syn. A. barbadensis, leaf juice; the fruit of bitter melon/karela (Momordica charantia) (found to improve glucose tolerance without increasing insulin levels); and the seeds of fenugreek (Trigonella foenum-graecum), are commonly used herbs with documented hypoglycemic effects. Also, two clinical studies with a water-soluble acidic fraction of an ethanol extract of gurmar (Gymnema sylvestre) leaves have reportedly reduced insulin requirements in both T1DM and T2DM, effects comparable to those observed with Aloe vera juice and glibenclamide. Antidiabetic effect of fenugreek is attributed to intestinal effects of the gum fiber (galactomannans), which also displays hypocholesterolemic activity.[6] Ginseng has hypoglycemic activity in patients with diabetes and this effect might be additive in patients taking oral hypoglycemics or insulin. The effect of these supplements is unpredictable in individuals and no specific changes in hypoglycemic doses are needed unless blood glucose changes occur.[44,45] While additive effects are certainly possible when these herbs are combined with the hypoglycemic drugs, appropriate self monitoring by the patient and clear lines of communication between the patient and health care practitioner should avert problems.

CONCLUSION

It is concluded that there is an alarming rate of prevalence and incident of drug interactions which is much higher in patients receiving combinations of drugs or poly-pharmacy or suffered from co-morbidity of diseases such as diabetes, hypertension, peptic ulcer, fungal infections and neurodegenerative disorders, which require prolong and multi treatments and the risk of drug interaction will increase as they are treated with multi-therapies. It is well reported that diabetic patients are suffering because of higher risk of drug interaction as they receive combination of therapies for diabetic complications as well, and hence the rate of occurrence of drug interaction is rapidly increases. As per our literature survey, we have found that the patients receiving diabetic medication are at higher

risk of drug-drug and drug-food interactions as they are receiving multitherapies for the treatment of diabetic complications and other related disorders. So that the physician and other medical staff should aware and guide the patient about the medication, drug related problems, interaction with food and other drugs or with medication. This will help to prevent and stop the occurrence of the drug-drug and drug-food interactions related to antidiabetic therapy. This review study summarized and highlights the various drug interactions likely drug-drug and drug-food interactions as well as reports unwanted effects of other treatment associated with antidiabetic agents in the diabetic patients.

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