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Pharmacokinetic and Pharmacodynamic Interactions of Sulfonylurea Antidiabetics

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Abstract

Sulfonylureas are useful to treat type 2 diabetes patients. Apart from sulfonylureas, the patients with diabetes may use many other medications to treat various concomitant illnesses such as high blood pressure, higher lipids, infections, pain, etc. The probability of interactions increases with the number of drugs used concomitantly. Most of the adverse drug interactions of sulfonylureas result in hypoglycemia, which can be life threatening. Sulfonylureas are primarily metabolized by CYP2C9 enzyme, which paves the way for most of their pharmacokinetic drug interactions. Drugs inhibiting CYP2C9 enzyme are expected to elevate the plasma concentrations of sulfonylureas and subsequent hypoglycemic complications. Some drugs potentiate the hypoglycemic activity of sulfonylureas pharmacodynamically too. The prescribers and pharmacists must be aware of the adverse drug interactions of sulfonylureas to prevent hypoglycemic episodes.

Keywords: Sulfonylurea, Pharmacokinetic interactions, Pharmacodynamic interactions, CYP2C9.

1. Introduction

Diabetes is a group of metabolic disorders occurring due to decreased insulin secretion/activity or both (ADA, 2014). According to first WHO Global report on diabetes, 422 million adults are living with diabetes worldwide and the number is increasing (WHO, 2016). The prevalence of diabetes is increasing and it is estimated that 552 million adults would be affected by diabetes by the year 2030 (Whiting et al., 2011), 592 million by the year 2035 (Guariguata et al., 2014) and 642 million by the year 2040 (Ogurtsova et al., 2017), globally.

Sulfonylureas are insulin secretagogues and may be used as second-line drugs to treat type 2 diabetes patients, in certain patients (Zhang et al., 2014). Sulfonylureas include first-generation drugs (Tolbutamide, Chlorpropamide, etc.), second-generation drugs (Gliclazide, Glipizide, Glibenclamide) (Sola et al., 2015) and third-generation drug (Glimepiride) (Ma et al., 2010; Inukai et al., 2005; Ueba et al., 2005). The second and third generation sulfonylureas are more potent than first-generation drugs (Melander, Wåhlin-Boll, 1982). Sulfonylureas bind to Sulfonylurea receptors leading to the closure of ATP-sensitive K^+-channel, inhibition of K^+ efflux, depolarization of cell membrane and opening of voltage-gated calcium channels. Increased intracellular calcium concentrations leads to the release of insulin (Henquin, 2017; Panten et al., 1996; Ashcroft, 1996).

Interference of effects of one drug by the coadministered drug(s), herb(s) or food is referred as Drug interaction (Baxter, 2010). Cigarette smoking and alcohol consumption too affect the fate of drugs. Drugs' effects are also affected by chronic disorders including liver and kidney diseases. Concurrent administration of two or more drugs results either in elevated risk of adverse effects or

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decreased therapeutic efficacy (Rowland, Matin, 1973). The drug interaction results in undesirable effects is termed “Adverse Drug Interaction”.

2. Methods

The databases such as Medline/PMC/PubMed, Google Scholar, Science Direct, Directory of open access journals (DOAJ) and reference lists were searched to identify related articles using the keywords Drug Interactions, Sulfonylureas, Pharmacodynamic Interactions, Pharmacokinetic Interactions and CYP2C9 enzyme.

3. Results and Discussion

Sulfonylurea antidiabetics have been identified to interact with various drugs pharmacokinetically or pharmacodynamically.

Pharmacokinetic drug interactions:

Increasing or decreasing the concentration of one drug in the system by another coadministered drug through the changes in absorption, distribution, metabolism, or excretion, is known as Pharmacokinetic interaction (Cascorbi, 2012). The bioavailability, volume of distribution, peak concentration, metabolism, clearance and half life, etc. of drugs are affected by pharmacokinetic drug interactions leading to changes in plasma concentrations. Various drugs have been identified to interact with sulfonylureas pharmacokinetically (Table 1).

Absorption Interactions:

The absorption of sulfonylureas altered by the concomitant use of drugs such as antacids containing magnesium salts and bile acid sequestrants.

Magnesium salts containing antacids:

Sulfonylureas are weakly acidic drugs and they are not ionized at gastric pH. However, administration of magnesium containing antacids elevates the gastric pH and increases solubility and absorption of sulfonylureas, which may result in hypoglycemia. To avoid this interaction, it is advised to administer sulfonylureas at least 1 hour before taking antacids (Neuvonen, Kivistö, 1994).

Bile acid sequestrants:

Sulfonylureas undergo enterohepatic circulation and the presence of cholestyramine in the gastrointestinal tract interrupts the enterohepatic circulation and enhances the elimination of sulfonylureas resulting in decreased intestinal absorption of sulfonylureas (May, Schindler, 2016; Kivisto, Neuvonen, 1990) and it is recommended to take sulfonylureas before 1-2 hours of administration of cholestyramine. In addition, the patients are advised to take glyburide 4 hours prior to colesevelam (Brown et al., 2010; Takebayashi et al., 2010).

Metabolism interactions:

Cytochrome P450 2C9 (CYP2C9) enzyme is primarily involved in the metabolism of sulfonylureas (Holstein et al., 2012). To a lesser extent, CYP3A4 enzyme is also involved in the sulfonylurea metabolism (Holstein, Beil, 2009). The drugs inducing or inhibiting CYP2C9 or CYP3A4 enzymes expected to result in decreased therapeutic efficacy or increased incidence of sulfonylurea-associated hypoglycemia.

CYP enzyme Inducers:

CYP enzyme inducers such as rifampicin and St John's Wort may decrease the plasma concentrations of sulfonylureas and hence their therapeutic efficacy. The blood glucose levels required to be monitored and the dosage adjustments may be necessary during concomitant use of sulfonylureas and CYP enzyme inducers.

Rifampicin:

Rifampicin is an inducer of CYP enzymes including CYP2C9 and CYP3A4, which usually metabolise sulfonylureas (Glaeser et al., 2005; Kanebratt et al., 2008). Administration of rifampicin in patients taking sulfonylureas may result in decreased exposure and reduced therapeutic efficacy of sulfonylureas, moderately (Niemi et al., 2001; Park et al., 2003). Monitoring

of blood glucose and dosage adjustments of sulfonylureas may be required if these drugs used concurrently (Surekha et al., 1997).

St John's Wort (*Hypericum perforatum)*:

St John's Wort is an antidepressant herb and it has the ability of inducing CYP enzymes (Wang et al., 2001). St John's Wort may accelerate the metabolism of sulfonylureas and reduce their plasma concentrations through the induction of CYP enzymes (Xu et al., 2008). Caution is advised in patients taking sulfonylureas and St John's Wort together.

CYP enzyme Inhibitors:

CYP2C9 enzyme inhibitors such as fibrates, azole antifungals, sulfonamides, isoniazid, metronidazole, cimetidine, fluvoxamine, and warfarin may elevate the plasma concentrations of sulfonylureas and subsequent hypoglycemic risk (Figure 1). It is recommended to advise the patients to monitor the signs and symptoms of hypoglycemia, while using sulfonylureas and CYP inhibitors concurrently.

Fibrates:

Fibrates such as gemfibrozil and fenofibrate can inhibit CYP2C9 enzyme and increase the plasma concentrations of sulfonylureas (Niemi et al., 2001). The plasma concentrations of sulfonylureas may also be elevated by reduced hepatic clearance of sulfonylureas resulting from fibrates induced inhibition of organic anion transporter polypeptides (OATPs) mediated hepatic uptake (Schelleman et al., 2014). Fibrates also found to be weak agonists of Peroxisome Proliferator-Activated Receptor (PPARα) and they can improve insulin resistance by affecting lipid and lipoprotein metabolism (Gross, Staels, 2007). The hypoglycemic risk is enhanced in patients taking sulfonylureas and fibrates concomitantly (Leonard et al., 2016).

Azole antifungals:

Azole antifungals such as voriconazole, miconazole, ketoconazole, fluconazole, etc. can inhibit CYP enzymes like CYP2B6, CYP2C9, CYP2C19 and CYP3A4 (Jeong et al., 2009; Hyland et al., 2003). Azole antifungals can interfere with the metabolism of sulfonylureas by inhibiting CYP enzymes and the risk of hypoglycemia is enhanced in diabetics taking sulfonylureas and azole antifungals concurrently (Shobha, Muppidi, 2010; Schelleman et al., 2010; Lomaestro, Piatek, 1998). Exercise caution in patients taking sulfonylureas and azole antifungals concomitantly (Kumar et al., 2013).

Sulfonamides:

Sulfonamides like sulfaphenazole, sulfadiazine, sulfamethizole, sulfisoxazole, sulfaphenazole, and sulfamethoxazole are potent inhibitors of CYP2C9 (Komatsu et al., 2000). Hypoglycemia risk is enhanced by the coadministration of sulfonamides with sulfonylureas (Tan et al., 2014). Patients taking sulfonylureas and sulfonamides together should be monitored for the signs and symptoms of hypoglycemia (Ho, Juurlink, 2011).

Isoniazid:

Isoniazid is a potent inhibitor of cytochrome P450 isozymes such as CYP2C9, CYP2C19 and CYP2E1 (Self et al., 1999). The risk of hypoglycemia may be enhanced in patients taking sulfonylureas and isoniazid concurrently (Boglou et al., 2013). The patients using sulfonylureas and isoniazid should be monitored for signs and symptoms of hypoglycemia.

Metronidazole:

Metronidazole is a CYP2C9 inhibitor (Covvey, Lewis, 2010). Administration of metronidazole in patients taking sulfonylureas may result in increased plasma levels of sulfonylureas and subsequent hypoglycemia (Parekh et al., 2014).

Cimetidine:

Cimetidine is an inhibitor of hepatic cytochrome P450 (CYP) enzymes (Levine, Bellward, 1995) and it's concomitant use with sulfonylureas may result in decreased metabolism of sulfonylureas and subsequent rise of plasma concentrations and hypoglycemia (Kubacka et al.,

1987). Monitoring of blood glucose and dosage adjustments are recommended (Archambeaud-Mouveroux et al., 1987).

Fluvoxamine:

Fluvoxamine is a Selective Serotonin Reuptake Inhibitor (SSRI) and it can inhibit the CYP2C9-mediated drug metabolism (Hemeryck et al., 1999). Concomitant use of fluvoxamine and sulfonylureas may result in hypoglycemia due to the inhibition of CYP2C9-mediated metabolism of sulfonylureas by fluvoxamine (Madsen et al., 2001). Monitor signs and symptoms of hypoglycemia if fluvoxamine and sulfonylureas used concurrently (Schmider et al., 1997).

Warfarin:

S-Warfarin is a substrate of CYP2C9 enzyme (Shaik et al., 2016). The risk of hypoglycemia is elevated in patients taking sulfonylureas when warfarin is added. The plasma drug concentrations of sulfonylureas elevated by warfarin, which displaces the sulfonylureas from protein binding and larger doses of warfarin, inhibits CYP2C9 mediated metabolism of sulfonylureas resulting in hypoglycemia (Romley et al., 2015).

Phenytoin:

Phenytoin is metabolized by CYP2C9 enzyme (Bajpai et al., 1996). Sulfonylureas can inhibit the metabolism of CYP2C9 substrate phenytoin (Kim, Park, 2003). Concomitant use of sulfonylureas and phenytoin may result in phenytoin toxicity including severe bradycardia and hypotension (Srinivasan et al., 2015; Beech et al., 1988).

Clopidogrel:

Clopidogrel is a prodrug and it's bioactivation depends on CYP enzymes including CYP2C9 (Brandt et al., 2007). Coadministration of sulfonylureas with clopidogrel may result in decreased clopidogrel bioactivation and reduced platelet inhibition (Harmsze et al., 2011). Ticagrelor can be substituted with clopidogrel if the patients need sulfonylureas and antiplatelet therapy together (Wang et al., 2015).

Clarithromycin:

Sulfonylureas including glibenclamide are the substrates of P-glycoprotein transporters (Golstein et al., 1999) and Clarithromycin is found to be the potent inhibitor of P-glycoprotein transporters (Eberl et al., 2007). Concurrent use of clarithromycin and sulfonylureas resulted in hypoglycemia (Bussing, Gende, 2002; Jayasagar et al., 2000).

Pharmacodynamic drug interactions:

The change of effect of one drug in presence of other drug(s) acting at the same site, same organ or different organ is called pharmacodynamic interaction. It can be additive, synergistic, potentiation or antagonistic interactions (Hinder, 2011). Sulfonylureas may interact pharmacodynamically with the drugs having some hypoglycemic potential (Figure 2 and Table 2).

ACE Inhibitors:

ACE inhibitors like captopril, enalapril, etc. increase the insulin sensitivity in presence of sulfonylureas (Rave et al., 2005). The incidence of hypoglycemic episodes reported to be higher in patients with type 2 diabetes taking ACE inhibitors and sulfonylureas concurrently (Herings et al., 1995; Shorr et al., 1997; Girardin, Raccah, 1998). Monitoring of blood glucose is recommended (Thamer et al., 1999).

Beta-adrenergic blockers:

Non-selective beta-adrenergic blockers such as propronolol, nadolol, etc. potentiate the hypoglycemic effects of sulfonylureas through the inhibition of glycogenolysis, gluconeogenesis and lipolysis and the stimulation of glucose uptake (Aziz et al., 1996; Groop, Neugebauer, 1996; Gaafar et al., 1994). Cardioselective beta blockers such as atenolol, metoprolol, etc. are preferred in patients with diabetes (Sinclair et al., 1990). Beta-blockers can mask the important signs and symptoms of hypoglycemia such as tachycardia, tremors and shakes.

Disopyramide:

Disopyramide is a class Ia antiarrhythmic drug and it is indicated for the treatment of ventricular and supraventricular arrhythmias. The blood glucose may be reduced by disopyramide through the inhibition of ATP-sensitive K^+-channel of β-cells and stimulation of insulin release. More potent and almost complete inhibition of K^+-channels occurs when disopyramide and sulfonylureas are administered together which may result in elevated risk of hypoglycemia. Caution is advised and monitoring of blood glucose is warranted when disopyramide and sulfonylureas are used concomitantly (Negishi et al., 2009).

Aspirin:

Aspirin is an antiplatelet drug and daily use of aspirin is recommended in high-risk patients to prevent heart attacks, strokes and blood clots. Aspirin may increase the effectiveness of sulfonylureas and elevate risk of hypoglycemia. Concomitant use of aspirin and sulfonylureas warrants monitoring of blood glucose (Patel et al., 2014; Fendrick et al., 2008; Cattaneo et al., 1990; Arena et al., 1978).

Phenylbutazone:

Phenylbutazone is a NSAID (Non-steroidal anti-inflammatory drug) and is not widely used due to its dangerous adverse effects such as agranulocytosis (Etess, Jacobson, 1953), hepatic lesions (Benjamin et al., 1981), and renal complications (Weisman, Bloom, 1955; Lipsett, Goldman, 1954), etc. However, some dietary supplements promoted for the treatment of arthritis and back pain may contain phenylbutazone as undeclared ingredient (Ries, Sahud, 1975). The elimination of sulfonylureas such as Acetohexamide, Chlorpropamide, Tobutamide, etc. can be decreased and their hypoglycemic activity potentiated by the administration of Phenylbutazone (Nomura et al., 1990; Shah et al., 1984; Szita et al., 1980; Ober, 1974).

Fluoroquinolones:

Fluoroquinolone antibacterials such as gatifloxacin, levofloxacin, etc. are able to enhance the insulin secretion (Bansal et al., 2015; Ghaly et al., 2009). The hypoglycemic risk is higher in patients taking fluoroquinolones and sulfonylureas together. The blood glucose level should be monitored closely and the dose of sulfonylureas needed to be adjusted during initiation and discontinuation of a fluoroquinolone (Garber et al., 2009; Lin et al., 2004; LeBlanc et al., 2004; Roberge et al., 2000).

4. Conclusion

The number of patients affected by diabetes is increasing yearly and the diabetics are prescribed with many medications to treat comorbidities such as hypertension, hyperlipidemia, etc., along with antidiabetic drugs. The patients may also take medications to treat infections, pain, etc. and some herbal supplements to help reducing blood sugar. The probability of drug interactions is higher in patients taking many medications. Most of the adverse drug interactions of sulfonylureas result in hypoglycemia, which can be life threatening. Pharmacokinetic drug interactions of sulfonylureas may occur mainly due to the inhibition of CYP2C9 mediated metabolism of sulfonylureas. Drugs such as Fibrates, Azole antifungals, Sulfonamides, Isoniazid, Metronidazole, Cimetidine, Fluvoxamine, etc. inhibit CYP2C9 enzyme and increase the plasma concentrations of sulfonylureas and the risk of subsequent hypoglycemic complications. Some drugs like Pioglitazone, Dulaglutide, ACE inhibitors, Beta blockers, Aspirin, Disopyramide, Fluoroquinolones, etc. potentiate the hypoglycemic activity of sulfonylureas pharmacodynamically. The prescribers and pharmacists must be aware of the adverse drug interactions of sulfonylureas to prevent hypoglycemic episodes. They may consider using alternative drugs and if concomitant use is necessary, the patients should be monitored for signs and symptoms of hypoglycemia including sweating, restlessness, confusion, irritability, palpitations, dizziness, blurred vision, seizures, unconsciousness, etc.

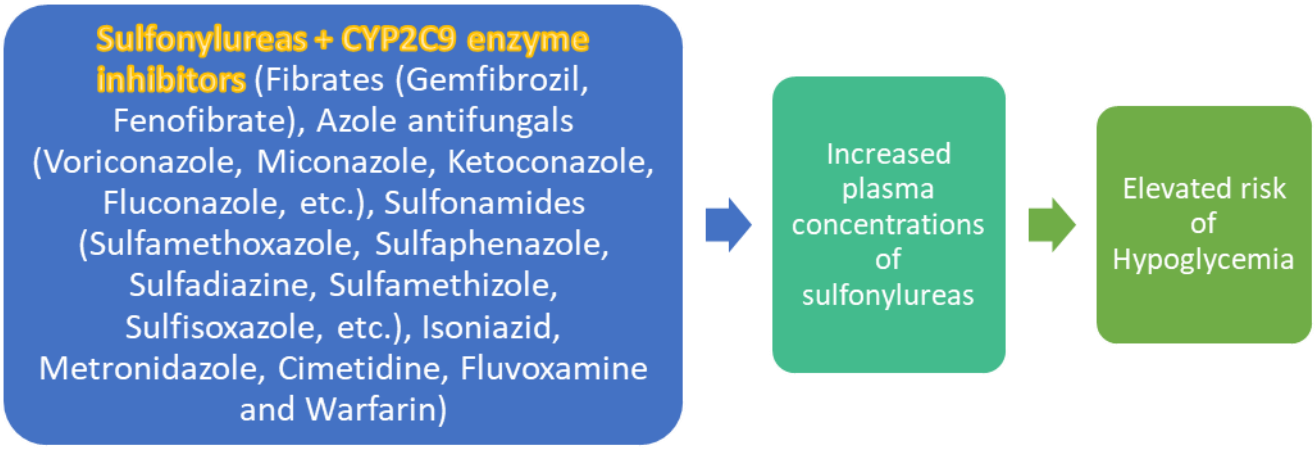

Fig. 1. Pharmacokinetic Drug Interactions of Sulfonylureas

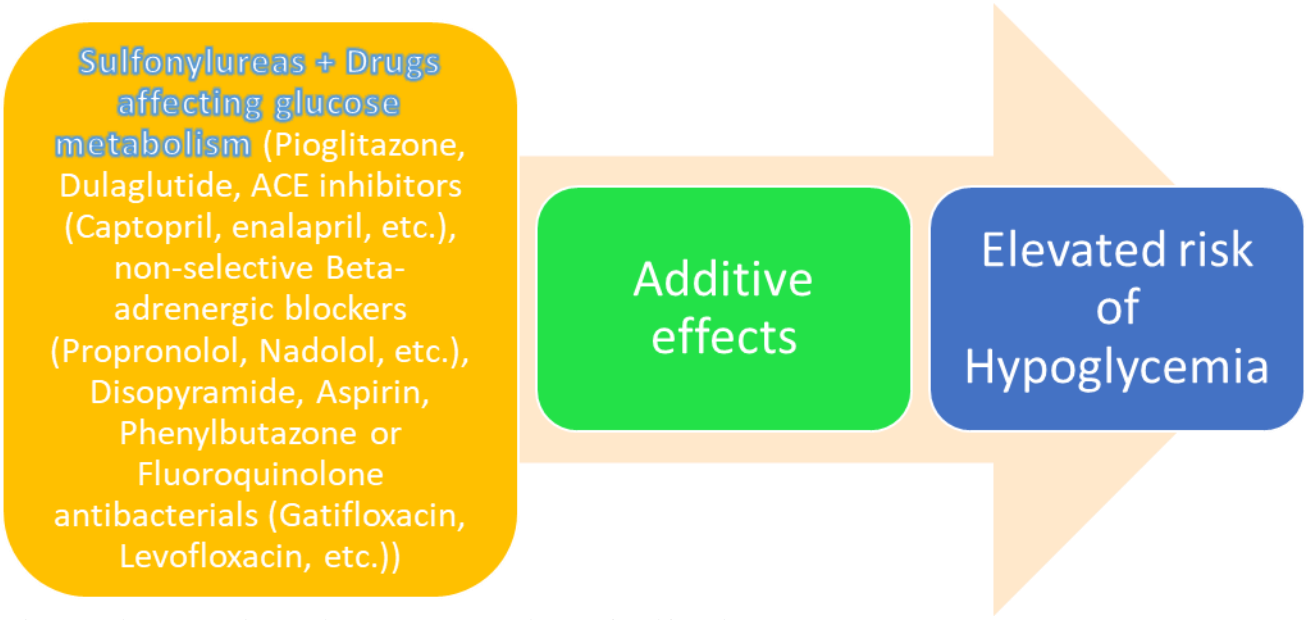

Fig. 2. Pharmacodynamic Drug Interactions of Sulfonylureas

Table 1. Pharmacokinetic interactions of Sulfonylureas

Interacting Drugs	**Mechanism of Interaction**	**Comments**
Magnesium containing **antacids**	Magnesium containing antacids elevate the gastric pH and increase solubility and absorption of sulfonylureas (Neuvonen et al., 1994).	Administer sulfonylureas at least 1 hour before taking antacids to avoid hypoglycemia.
Bile acid sequestrants (Cholestyramine)	Cholestyramine interrupts the enterohepatic circulation and decreases the intestinal absorption of sulfonylureas (Kivisto, Neuvonen, 1990).	Take sulfonylureas before 1-2 hours of administration of cholestyramine.
Rifampin	The therapeutic efficacy of sulfonylureas may be decreased by rifampin,	Monitoring of blood glucose and dosage adjustments of sulfonylureas may be required (Surekha et al., 1997).

	which induces CYP2C9, CYP3A4 and P-glycoprotein (Niemi et al., 2001; Park et al., 2003).	
St John's Wort	St John's Wort may reduce the plasma concentrations of sulfonylureas through the induction of CYP enzymes (Xu et al., 2008).	Monitor the patients closely for the possible signs of reduced sulfonylureas efficacy.
Fibrates (Gemfibrozil, Fenofibrate)	Fibrates such as can inhibit CYP2C9 enzyme and increase the plasma concentrations of sulfonylureas (Niemi et al., 2001a).	The risk of hypoglycemic is enhanced in patients taking sulfonylureas and fibrates concomitantly (Leonard et al., 2016).
Azole antifungals (Voriconazole, Miconazole, Ketoconazole, Fluconazole, etc.)	Azole antifungals can interfere with the metabolism of sulfonylureas by inhibiting CYP enzymes (CYP2C9 and CYP3A4) (Shobha JC, Muppidi MR, 2010 ; Schelleman H et al., 2010 ; Lomaestro BM, Piatek MA, 1998).	Exercise caution in patients taking sulfonylureas and azole antifungals concomitantly (Kumar et al., 2013).
Sulfonamides (Sulfamethoxazole, Sulfaphenazole, Sulfadiazine, Sulfamethizole, Sulfisoxazole, etc.)	Sulfonamides enhance the plasma concentrations of sulfonylureas by inhibiting their CYP2C9 mediated metabolism (Tan et al., 2014).	Patients taking sulfonylureas and sulfonamides together should be monitored for the signs and symptoms of hypoglycemia (Ho, Juurlink, 2011).
Isoniazid	Isoniazid can inhibit CYP2C9 mediated metabolism of sulfonylureas and elevate their plasma concentrations (Boglou et al., 2013).	The patients using sulfonylureas and isoniazid should be monitored for signs and symptoms of hypoglycemia.
Metronidazole	Metronidazole is a CYP2C9 inhibitor and administration of metronidazole in patients taking sulfonylureas may result in increased plasma levels of sulfonylureas (Covvey, Lewis, 2010).	Monitor the patients for signs and symptoms of hypoglycemia.
Cimetidine	Cimetidine is an inhibitor of hepatic cytochrome P450 (CYP) enzymes and its concomitant use with sulfonylureas may result in decreased metabolism of sulfonylureas and subsequent rise of plasma	Monitoring of blood glucose and dosage adjustments are recommended (Archambeaud-Mouveroux et al., 1987).

	concentrations and hypoglycemia (Kubacka RT et al., 1987).	
Fluvoxamine	Fluvoxamine can inhibit the CYP2C9-mediated metabolism resulting in hypoglycemia (Madsen et al., 2001).	Monitor signs and symptoms of hypoglycemia if fluvoxamine and sulfonylureas used concurrently (Schmider et al., 1997).
Warfarin	S-Warfarin is a substrate of CYP2C9 enzyme and the risk of hypoglycemia is elevated in patients taking sulfonylureas when warfarin is added (Shaik AN et al., 2016).	It is recommended to monitor the signs and symptoms of hypoglycemia.
Phenytoin	Sulfonylureas can inhibit CYP2C9 mediated metabolism of phenytoin (Kim, Park, 2003).	Concomitant use of sulfonylureas and phenytoin may result in phenytoin toxicity including severe bradycardia and hypotension (Srinivasan et al., 2015; Beech E et al., 1988).
Clopidogrel	Sulfonylureas inhibit CYP2C9-mediated bioactivation of clopidogrel resulting in reduced platelet inhibition (Harmsze et al., 2011).	Ticagrelor can be substituted with clopidogrel if the patients need sulfonylureas and antiplatelet therapy together (Wang et al., 2015).
Clarithromycin	Clarithromycin can elevate the plasma levels of sulfonylureas by inhibiting P-glycoprotein transporters (Bussing, Gende, 2002; Jayasagar et al., 2000).	Concurrent use of clarithromycin and sulfonylureas resulted in hypoglycemia.

Table 2. Pharmacodynamic interactions of Sulfonylureas

Interacting Drugs	**Mechanism of Interaction**	**Comments**
ACE inhibitors (Captopril, Enalapril, etc)	ACE inhibitors can increase the insulin sensitivity in presence of sulfonylureas (Herings et al., 1995 ; Shorr et al., 1997 ; Girardin, Raccah, 1998).	The incidence of hypoglycemic episodes reported to be higher in patients with type 2 diabetes taking ACE inhibitors and sulfonylureas concurrently. Monitor the blood glucose (Thamer et al., 1999).
Non-selective **beta-adrenergic blockers** (Propronolol, Nadolol, etc.)	Non-selective beta-adrenergic blockers potentiate the hypoglycemic effects of sulfonylureas through the inhibition of glycogenolysis, gluconeogenesis and lipolysis and the stimulation of glucose uptake (Aziz et al., 1996; Groop, Neugebauer, 1996; Gaafar et al., 1994).	Cardioselective beta blockers such as atenolol, metoprolol, etc. are preferred in patients with diabetes (Sinclair et al., 1990).

Disopyramide	The blood glucose may be reduced by disopyramide through the inhibition of ATP-sensitive K^+-channel of β-cells and stimulation of insulin release. More potent and almost complete inhibition of K^+-channels occurs when disopyramide and sulfonylureas are administered together which may result in elevated risk of hypoglycemia (Negishi et al., 2009).	Caution is advised and monitoring of blood glucose is warranted when disopyramide and sulfonylureas are used concomitantly (Negishi et al., 2009).
Aspirin	Aspirin may increase the effectiveness of sulfonylureas and elevate risk of hypoglycemia (Patel et al., 2014; Fendrick et al., 2008; Cattaneo et al., 1990; Arena et al., 1978).	Concomitant use of aspirin and sulfonylureas warrants monitoring of blood glucose.
Phenylbutazone	The elimination of sulfonylureas such as Acetohexamide, Chlorpropamide, Tobutamide, etc. can be decreased and their hypoglycemic activity potentiated by the administration of Phenylbutazone (Nomura et al., 1990 ; Shah et al., 1984; Szita et al., 1980; Ober, 1974).	Monitor blood glucose if concomitant use is necessary.
Fluoroquinolone antibacterials (Gatifloxacin, Levofloxacin, etc.)	Fluoroquinolone antibacterials are able to enhance the insulin secretion. The hypoglycemic risk is higher in patients taking fluoroquinolones and sulfonylureas together (Bansal et al., 2015; Ghaly et al., 2009).	The blood glucose level should be monitored closely and the dose of sulfonylureas needed to be adjusted during initiation and discontinuation of a fluoroquinolone (Garber et al., 2009; Lin et al., 2004; LeBlanc et al., 2004; Roberge et al., 2000).

References

ADA, 2014 – American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2014 Jan 1; 37 (Supplement 1): S81-90.

Archambeaud-Mouveroux F et al., 1987 – *Archambeaud-Mouveroux F, Nouaille Y, Nadalon S, Treves R, Merle L.* (1987). Interaction between gliclazide and cimetidine. *European journal of clinical pharmacology*. 31(5): 631.

Arena et al., 1978 – *Arena F.P., Dugowson C., Saudek C.D.* (1978). Salicylate-induced hypoglycemia and ketoacidosis in a nondiabetic adult. *Archives of internal medicine*. 138(7): 1153-4.

Ashcroft, 1996 – *Ashcroft F.M.* (1996). Mechanisms of the glycaemic effects of sulfonylureas. Hormone and metabolic research. 28(09): 456-63.

Aziz et al., 1996 – *Aziz A.A., Moustafa A.M., Ellah M.A., El-Mazar M.A.* (1996). Nadolol–Glibenclamide Interaction: Relevance To Carbohydrate Metabolism In Hyperglycaemic Rats. *Pharmacological research*. 34(1): 11-5.

Bajpai et al., 1996 – *Bajpai M., Roskos L.K., Shen D.D., Levy R.H.* (1996). Roles of cytochrome P4502C9 and cytochrome P4502C19 in the stereoselective metabolism of phenytoin to its major metabolite. Drug Metabolism and Disposition. 24(12): 1401-3.

Bansal et al., 2015 – *Bansal N., Manocha D., Madhira B.* (2015). Life-Threatening Metabolic Coma Caused by Levofloxacin. *American journal of therapeutics*. 22(2): e48-51.

Baxter, 2010 – *Baxter K.* (2010). Stockley's drug interactions. Preston CL, editor. London: Pharmaceutical Press.

Beech et al., 1988 – *Beech E., Mathur S.V., Harrold B.P.* (1988). Phenytoin toxicity produced by tolbutamide. *BMJ: British Medical Journal*. 297(6663): 1613.

Benjamin et al., 1981 – *Benjamin S.B., Ishak K.G., Zimmerman H.J., Grushka A.* (1981). Phenylbutazone liver injury: A clinical-pathologic survey of 23 cases and review of the literature. Hepatology. 1(3): 255-63.

Boglou et al., 2013 – *Boglou P., Steiropoulos P., Papanas N., Bouros D.* (2013). Hypoglycaemia due to interaction of glimepiride with isoniazid in a patient with type 2 diabetes mellitus. *BMJ case reports*. 2013: bcr2012008528.

Brandt et al., 2007 – *Brandt J.T., Close S.L., Iturria S.J., Payne C.D., Farid N.A., Ernest C.S., Lachno D.R., Salazar D., Winters K.J.* (2007). Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *Journal of Thrombosis and Haemostasis*. 5(12): 2429-36.

Brown et al., 2010 – *Brown K.S., Armstrong I.C., Wang A., Walker J.R., Noveck R.J., Swearingen D., Allison M., Kissling J.C., Kisicki J., Salazar D.E.* (2010). Effect of the bile acid sequestrant colesevelam on the pharmacokinetics of pioglitazone, repaglinide, estrogen estradiol, norethindrone, levothyroxine, and glyburide. *The Journal of Clinical Pharmacology*. 50(5): 554-65.

Bussing, Gende, 2002 – *Bussing R., Gende A.* (2002). Severe hypoglycemia from clarithromycin-sulfonylurea drug interaction. *Diabetes Care*. 25(9): 1659-61.

Cascorbi, 2012 – *Cascorbi I.* (2012). Drug interactions—principles, examples and clinical consequences. *Deutsches Ärzteblatt International*. 109(33-34): 546.

Cattaneo et al., 1990 – *Cattaneo A.G, Caviezel F., Pozza G.* (1990). Pharmacological interaction between tolbutamide and acetylsalicylic acid: study on insulin secretion in man. *International journal of clinical pharmacology, therapy, and toxicology*. 28(6): 229-34.

Covvey, Lewis, 2010 – *Covvey J.R., Lewis D.A.* (2010). Glimepiride-induced hypoglycemia with ciprofloxacin, metronidazole, and acute kidney injury. *Hospital Pharmacy*. 45(12): 934-8.

Eberl et al., 2007 – *Eberl S., Renner B., Neubert A., Reisig M., Bachmakov I., König J., Dörje F., Mürdter T.E., Ackermann A., Dormann H., Gassmann K.G.* (2007). Role of P-glycoprotein inhibition for drug interactions. *Clinical pharmacokinetics*. 46(12): 1039-49.

Etess, Jacobson, 1953 – *Etess A.D., Jacobson A.S.* (1953). Fatality Due to Agranulocytosis Following Use of Phenylbutazone (Butazolidin®). *Journal of the American Medical Association*. 151(8): 639-40.

Fendrick et al., 2008 – *Fendrick A.M., Pan D.E., Johnson G.E.* (2008). OTC analgesics and drug interactions: clinical implications. *Osteopathic medicine and primary care*. 2(1): 2.

Gaafar et al., 1994 – *Gaafar K., Salama S., El Batran S.* (1994). Studies on the glycemic and lipidemic effect of atenolol and propranolol in normal and diabetic rats. *Arzneimittel-Forschung*. 44(4): 496-501.

Garber et al., 2009 – *Garber S.M., Pound, M.W., Miller, S.M.* (2009). Hypoglycemia associated with the use of levofloxacin. *American Journal of Health-System Pharmacy*, 66(11).

Ghaly et al., 2009 – *Ghaly H., Kriete C., Sahin S., Pflöger A., Holzgrabe U., Zünkler B.J., Rustenbeck I.* (2009). The insulinotropic effect of fluoroquinolones. *Biochemical pharmacology*. 77(6): 1040-52.

Girardin, Raccah, 1998 – *Girardin E, Raccah D.* (1998). Interaction between converting enzyme inhibitors and hypoglycemic sulfonamides or insulin. Presse medicale (Paris, France: 1983). 27(37): 1914-23.

Glaeser et al., 2005 – *Glaeser H., Drescher S., Eichelbaum M., Fromm M.F.* (2005). Influence of rifampicin on the expression and function of human intestinal cytochrome P450 enzymes. *British journal of clinical pharmacology*. 59(2): 199-206.

Golstein et al., 1999 – *Golstein P.E., Boom A., Van Geffel J., Jacobs P., Masereel B., Beauwens R.* (1999). P-glycoprotein inhibition by glibenclamide and related compounds. *Pflügers Archiv European Journal of Physiology*. 437(5): 652-60.

Groop, Neugebauer, 1996 – *Groop L., Neugebauer G.* (1996). Clinical pharmacology of sulfonylureas. InOral Antidiabetics 1996 (pp. 199-259). Springer Berlin Heidelberg.

Gross, Staels, 2007 – *Gross B., Staels B.* (2007). PPAR agonists: multimodal drugs for the treatment of type-2 diabetes. *Best Practice & Research Clinical Endocrinology & Metabolism*. 21(4): 687-710.

Guariguata et al., 2014 – *Guariguata L., Whiting D.R., Hambleton I., Beagley J., Linnenkamp U., Shaw J.E.* (2014). Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes research and clinical practice. 103(2): 137-49.

Harmsze et al., 2011 – *Harmsze A.M., Van Werkum J.W., Moral F., Ten Berg J.M., Hackeng C.M., Klungel O.H., De Boer A., Deneer V.H.* (2011). Sulfonylureas and on-clopidogrel platelet reactivity in type 2 diabetes mellitus patients. *Platelets*. 22(2): 98-102.

Hemeryck et al., 1999 – *Hemeryck A., De Vriendt C., Belpaire F.M.* (1999). Inhibition of CYP2C9 by selective serotonin reuptake inhibitors: in vitro studies with tolbutamide and (S)-warfarin using human liver microsomes. *European journal of clinical pharmacology*. 54(12): 947-51.

Henquin, 2017 – *Henquin J.C.* (2017). Misunderstandings and controversies about the insulin-secreting properties of antidiabetic sulfonylureas. *Biochimie*.

Herings et al., 1995 – *Herings R.M.C., De Boer, A., Leufkens, H.G.M., Porsius, A., Stricker, B.C.* (1995). Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *The Lancet*, 345(8959), pp. 1195-1198.

Hinder, 2011 – *Hinder M.* (2011). Pharmacodynamic drug–drug interactions. InDrug discovery and evaluation: methods in clinical pharmacology. Springer Berlin Heidelberg, pp. 367-376.

Ho, Juurlink, 2011 – *Ho J.M., Juurlink D.N.* (2011). Considerations when prescribing trimethoprim–sulfamethoxazole. *Canadian Medical Association Journal*. 183(16): 1851-8.

Holstein, Beil, 2009 – *Holstein A., Beil W.* (2009). Oral antidiabetic drug metabolism: pharmacogenomics and drug interactions. *Expert opinion on drug metabolism & toxicology*. 5(3): 225-41.

Holstein et al., 2012 – *Holstein A., Beil W., Kovacs P.* (2012). CYP2C metabolism of oral antidiabetic drugs-impact on pharmacokinetics, drug interactions and pharmacogenetic aspects. *Expert opinion on drug metabolism & toxicology*. 8(12): 1549-63.

Hyland et al., 2003 – *Hyland R., Jones B.C., Smith D.A.* (2003). Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. *Drug Metabolism and Disposition*. 31(5): 540-7.

Inukai et al., 2005 – *Inukai K., Watanabe M., Nakashima Y., Takata N., Isoyama A., Sawa T., Kurihara S., Awata T., Katayama S.* (2005). Glimepiride enhances intrinsic peroxisome proliferator-activated receptor-γ activity in 3T3-L1 adipocytes. *Biochemical and biophysical research communications*. 328(2) :484-90.

Jayasagar et al., 2000 – *Jayasagar G., Dixit A.A., Kishan V., Rao Y.M.* (2000). Effect of clarithromycin on the pharmacokinetics of tolbutamide. *Drug metabolism and drug interactions*. 16(3): 207-16.

Jeong et al., 2009 – *Jeong S., Nguyen P.D., Desta Z.* (2009). Comprehensive in vitro analysis of voriconazole inhibition of eight cytochrome P450 (CYP) enzymes: major effect on CYPs 2B6, 2C9, 2C19, and 3A. *Antimicrobial agents and chemotherapy*. 53(2): 541-51.

Kanebratt et al., 2008 – *Kanebratt K.P., Diczfalusy U., Bäckström T., Sparve E., Bredberg E., Böttiger Y., Andersson T.B., Bertilsson L.* (2008). Cytochrome P450 induction by rifampicin in healthy subjects: determination using the karolinska cocktail and the endogenous CYP3A4 marker 4β-hydroxycholesterol. *Clinical Pharmacology & Therapeutics*. 84(5): 589-94.

Kim, Park, 2003 – *Kim K.A., Park J.Y. (2003).* Inhibitory effect of glyburide on human cytochrome p450 isoforms in human liver microsomes. *Drug metabolism and disposition*. 31(9): 1090-2.

Kivisto KT, Neuvonen PJ, 1990 – *Kivisto K.T., Neuvonen PJ.* (1990). The effect of cholestyramine and activated charcoal on glipizide absorption. *British journal of clinical pharmacology*. 30(5): 733-6.

Komatsu et al., 2000 – *Komatsu K., Ito K., Nakajima Y., Kanamitsu S.I., Imaoka S., Funae Y., Green C.E., Tyson C.A., Shimada N., Sugiyama Y.* (2000). Prediction of in vivo drug-drug interactions between tolbutamide and various sulfonamides in humans based on in vitro experiments. *Drug Metabolism and Disposition*. 28(4): 475-81.

Kubacka et al., 1987 – *Kubacka R.T., Antal E.J., Juhl R.P.* (1987). The paradoxical effect of cimetidine and ranitidine on glibenclamide pharmacokinetics and pharmacodynamics. *British journal of clinical pharmacology*. 23(6): 743-51.

Kumar et al., 2013 – *Kumar B.H., Joshi B., Singh J.C, Diwan P.V.* (2013). Drug-drug interaction between voriconazole and oral hypoglycemic agents in diabetic rats. *Indian journal of pharmacology*. 45(2): 155.

LeBlanc et al., 2004 – *LeBlanc M., Bélanger C., Cossette P.* (2004). Severe and resistant hypoglycemia associated with concomitant gatifloxacin and glyburide therapy. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 24(7): 926-31.

Leonard et al., 2016 – *Leonard C.E., Bilker W.B., Brensinger C.M., Han X., Flory J.H., Flockhart D.A., Gagne J.J., Cardillo S., Hennessy S.* (2016). Severe hypoglycemia in users of sulfonylurea antidiabetic agents and antihyperlipidemics. *Clinical Pharmacology & Therapeutics*. 99(5): 538-47.

Levine, Bellward, 1995 – *Levine M., Bellward G.D.* (1995). Effect of cimetidine on hepatic cytochrome P450: evidence for formation of a metabolite-intermediate complex. *Drug metabolism and disposition*. 23(12): 1407-11.

Lin et al., 2004 – *Lin G., Hays D.P., Spillane L.* (2004). Refractory hypoglycemia from ciprofloxacin and glyburide interaction. *Journal of Toxicology: Clinical Toxicology*. 42(3): 295-7.

Lipsett, Goldman, 1954 – *Lipsett M.B., Goldman R.* (1954). Phenylbutazone toxicity: Report of a case of acute renal failure. *Annals of internal medicine*. 41(5): 1075-9.

Lomaestro, Piatek, 1998 – *Lomaestro B.M., Piatek M.A.* (1998). Update on drug interactions with azole antifungal agents. *Annals of Pharmacotherapy*. 32(9): 915-28.

Ma et al., 2010 – *Ma P., Gu B., Ma J., Lingling E., Wu X., Cao J., Liu H.* (2010). Glimepiride induces proliferation and differentiation of rat osteoblasts via the PI3-kinase/Akt pathway. Metabolism. 59(3): 359-66.

Madsen et al., 2001 – *Madsen H., Enggaard T.P., Hansen L.L., Klitgaard N.A., Brøsen K.* (2001). Fluvoxamine inhibits the CYP2C9 catalyzed biotransformation of tolbutamide. *Clinical Pharmacology & Therapeutics*. 69(1): 41-7.

May, Schindler, 2016 – *May M., Schindler C.* (2016). Clinically and pharmacologically relevant interactions of antidiabetic drugs. *Therapeutic advances in endocrinology and metabolism*. 7(2): 69-83.

Melander, Wåhlin-Boll, 1982 – *Melander A, Wåhlin-Boll E.* (1982). Clinical pharmacokinetics of sulfonylureas: a brief review. *Annals of clinical research*. 15: 12-5.

Negishi et al., 2009 – *Negishi M., Shimomura, K., Proks, P., Mori, M. and Shimomura, Y.* (2009). Mechanism of disopyramide-induced hypoglycaemia in a patient with Type 2 diabetes. *Diabetic Medicine*, 26(1): 76-78.

Neuvonen, Kivistö, 1994 – *Neuvonen P.J., Kivistö, K.T.* (1994). Enhancement of drug absorption by antacids. *Clinical pharmacokinetics*, 27(2), pp. 120-128.

Niemi et al., 2001 – *Niemi M., Backman J.T., Neuvonen M., Neuvonen P.J., Kivistö K.T.* (2001). Effects of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. *Clinical Pharmacology & Therapeutics*. 69(6): 400-6.

Niemi et al., 2001a – *Niemi M., Neuvonen P.J., Kivistö K.T.* (2001). Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of glimepiride. *Clinical Pharmacology & Therapeutics*. 70(5): 439-45.

Nomura et al., 1990 – *Nomura T., Katsuki Y., Kojima Y., Otagiri M.* (1990). Mechanism of pharmacodynamic and pharmacokinetic interactions between acetohexamide and phenylbutazone in rabbits. *Basic & Clinical Pharmacology & Toxicology*. 67(5): 415-9.

Ober, 1974 – *Ober K.F.* (1974). Mechanism of interaction of tolbutamide and phenylbutazone in diabetic patients. *European journal of clinical pharmacology*. 7(4): 291-4.

Ogurtsova et al., 2017 – *Ogurtsova K., da Rocha Fernandes J.D., Huang Y., Linnenkamp U., Guariguata L., Cho N.H., Cavan D., Shaw J.E., Makaroff L.E.* (2017). IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Research and Clinical Practice. 128: 40-50.

Panten et al., 1996 – *Panten U., Schwanstecher M., Schwanstecher C.* (1996). Sulfonylurea receptors and mechanism of sulfonylurea action. *Experimental and clinical endocrinology & diabetes*. 104(01): 1-9.

Parekh et al., 2014 – *Parekh T.M., Raji M., Lin Y.L., Tan A., Kuo Y.F., Goodwin J.S.* (2014). Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas. J*AMA internal medicine*. 174(10): 1605-12.

Park et al., 2003 – *Park J.Y., Kim K.A., Park P.W., Park C.W., Shin J.G.* (2003). Effect of rifampin on the pharmacokinetics and pharmacodynamics of gliclazide. *Clinical Pharmacology & Therapeutics*. 74(4): 334-40.

Patel et al., 2014 – *Patel P.S., Rana D.A., Suthar J.V., Malhotra S.D., Patel V.J.* (2014). A study of potential adverse drug-drug interactions among prescribed drugs in medicine outpatient department of a tertiary care teaching hospital. *Journal of basic and clinical pharmacy*. 5(2): 44.

Rave et al., 2005 – *Rave K., Flesch, S., Kühn-Velten, W.N., Hompesch, B.C., Heinemann, L., Heise, T. (*2005). Enhancement of blood glucose lowering effect of a sulfonylurea when coadministered with an ACE inhibitor: results of a glucose-clamp study. *Diabetes/metabolism research and reviews*, *21*(5): 459-464.

Ries, Sahud, 1975 – *Ries C.A., Sahud M.A.* (1975). Agranulocytosis caused by Chinese herbal medicines: dangers of medications containing aminopyrine and phenylbutazone. *JAMA*. 231(4): 352-5.

Roberge et al., 2000 – *Roberge R.J., Kaplan R., Frank R., Fore, C.* (2000). Glyburide-ciprofloxacin interaction with resistant hypoglycemia. *Annals of emergency medicine*, 36(2): 160-163.

Romley et al., 2015 – *Romley J.A., Gong C., Jena A.B., Goldman D.P., Williams B., Peters A.* (2015). Association between use of warfarin with common sulfonylureas and serious hypoglycemic events: retrospective cohort analysis. *BMJ*. 351: h6223.

Rowland, Matin, 1973 – *Rowland M., Matin S.B.* (1973). Kinetics of drug-drug interactions. *Journal of Pharmacokinetics and Pharmacodynamics*. 1(6): 553-67.

Schelleman et al., 2010 – *Schelleman H., Bilker W.B., Brensinger C.M., Wan F., Hennessy S.* (2010). Anti-Infectives and the Risk of Severe Hypoglycemia in Users of Glipizide or Glyburide. *Clinical Pharmacology & Therapeutics*. 88(2): 214-22.

Schelleman et al., 2014 – *Schelleman H., Han X., Brensinger C.M., Quinney S.K., Bilker W.B., Flockhart D.A., Li L, Hennessy S.* (2014). Pharmacoepidemiologic and in vitro evaluation of potential drug–drug interactions of sulfonylureas with fibrates and statins. *British journal of clinical pharmacology*. 78(3): 639-48.

Schmider et al., 1997 – *Schmider J., Greenblatt D.J., Von Moltke L.L., Karsov D., Shader R.I.* (1997). Inhibition of CYP2C9 by selective serotonin reuptake inhibitors in vitro: studies of phenytoin p-hydroxylation. *British journal of clinical pharmacology*. 144(5): 495-8.

Self et al., 1999 – *Self T.H., Chrisman C.R., Baciewicz A.M., Bronze M.S.* (1999). Isoniazid drug and food interactions. *The American journal of the medical sciences*. 317(5): 304-11.

Shah et al., 1984 – *Shah S.J., Bhandarkar S.D., Satoskar R.S.* (1984). Drug interaction between chlorpropamide and non-steroidal anti-inflammatory drugs, ibuprofen and phenylbutazone. *International journal of clinical pharmacology, therapy, and toxicology*. 22(9): 470-2.

Shaik et al., 2016 – *Shaik A.N., Grater R., Lulla M., Williams D.A., Gan L.L., Bohnert T., LeDuc B.W.* (2016). Comparison of enzyme kinetics of warfarin analyzed by LC–MS/MS QTrap and differential mobility spectrometry. *Journal of Chromatography B*. 1008: 164-73.

Shobha, Muppidi, 2010 – *Shobha J.C., Muppidi M.R.* (2010). Interaction between voriconazole and glimepiride. *Journal of postgraduate medicine*. 56(1): 44.

Shorr et al., 1997 – *Shorr R.I., Ray W.A., Daugherty J.R., Griffin M.R.* (1997). Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA*. 278(1): 40-3.

Sinclair et al., 1990 – *Sinclair A.J., Davies I.B., Warrington S.J.* (1990). Betaxolol and glucose-insulin relationships: studies in normal subjects taking glibenclamide or metformin. *British journal of clinical pharmacology*. 30(5): 699-702.

Sola et al., 2015 – *Sola D., Rossi L., Schianca G.P., Maffioli P., Bigliocca M., Mella R., Corlianò F., Fra G.P., Bartoli E., Derosa G.* (2015). Sulfonylureas and their use in clinical practice. *Archives of medical science: AMS*. 11(4): 840.

Srinivasan et al., 2015 – *Srinivasan G., Wyawahare M., Mathen P.G., Subrahmanyam D.K.* (2015). Life-threatening bradyarrhythmia with oral phenytoin overdose. Journal of pharmacology & pharmacotherapeutics. 6(3): 179.

Surekha et al., 1997 – *Surekha V., Peter J.V., Jeyaseelan L., Cherian A.M.* (1997). Drug interaction: rifampicin and glibenclamide. *National medical journal of India*. 10(1).

Szita et al., 1980 – *Szita M., Gachalyi B., Tornyossy M., Kaldor A.* (1980). Interaction of phenylbutazone and tolbutamide in man. *International journal of clinical pharmacology, therapy, and toxicology*. 18(9): 378-80.

Tan et al., 2014 – *Tan A, Holmes HM, Kuo YF, Raji MA, Goodwin JS.* (2014). Coadministration of co-trimoxazole with sulfonylureas: hypoglycemia events and pattern of use. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*. 70(2): 247-54.

Takebayashi et al., 2010 – *Takebayashi K., Aso Y., Inukai T.* (2010). Role of bile acid sequestrants in the treatment of type 2 diabetes. *World journal of diabetes*. 1(5): 146.

Thamer et al., 1999 – *Thamer M., Ray N.F., Taylor T.* (1999). Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clinical therapeutics*. 21(8): 1387-400.

Ueba et al., 2005 – *Ueba H., Kuroki M., Hashimoto S., Umemoto T., Yasu T., Ishikawa S.E., Saito M., Kawakami M.* (2005). Glimepiride induces nitric oxide production in human coronary artery endothelial cells via a PI3-kinase-Akt dependent pathway. *Atherosclerosis*. 183(1): 35-9.

Wang et al., 2001 – *Wang Z., Gorski J.C., Hamman M.A., Huang S.M., Lesko L.J., Hall S.D.* (2001). The effects of St John's wort (Hypericum perforatum) on human cytochrome P450 activity. *Clinical Pharmacology & Therapeutics*. 70(4): 317-26.

Wang et al., 2015 – *Wang Z.Y., Chen M., Zhu L.L., Yu L.S., Zeng S., Xiang M.X., Zhou Q.* (2015). Pharmacokinetic drug interactions with clopidogrel: updated review and risk management in combination therapy. *Therapeutics and Clinical Risk Management*. 11: 449.

Weisman, Bloom, 1955 – *Weisman J.I., Bloom B.* (1955). Anuria following phenylbutazone therapy. *New England Journal of Medicine*. 252(25): 1086-7.

Whiting et al., 2011 – *Whiting D.R., Guariguata L., Weil C., Shaw J.* (2011). IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes research and clinical practice*. 94(3): 311-21.

WHO, 2016 – World Health Organization. World Health Statistics 2016: Monitoring Health for the SDGs Sustainable Development Goals. World Health Organization; 2016 Jun 8.

Xu et al., 2008 – *Xu H., Williams K.M., Liauw W.S., Murray M., Day R.O., McLachlan A.J.* (2008). Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. *British journal of pharmacology*. 153(7): 1579-86.

Zhang et al., 2014 – *Zhang Y., McCoy R.G., Mason J.E., Smith S.A, Shah N.D., Denton B.T.* (2014). Second-line agents for glycemic control for type 2 diabetes: are newer agents better? *Diabetes Care*. 37(5): 1338-45.