Drug Interactions of antidiabetic drugs

Dr M. Abbasinazari
Professor of Clinical Pharmacy

- Patients with T2DM often do not suffer solely from symptoms of increased blood glucose levels.
- In the majority of cases, several comorbidities are present with the need of additional pharmacological treatment.
- Concomitant diseases such as HTN and HLP can lead to both microvascular and macrovascular complications. Moreover, central nervous disorders such as depression are increased in patients with T2DM compared with the general population
- Probability of Poly pharmacy in T2DM
- Most common clinically relevant drug–drug interactions with antidiabetic medications occur with SUs, saxagliptin and TZDs

Definition

- Adverse drug response produced by the administration of a drug or co exposure of the drug with another substance which modifies the patients response to the drug

Precipitant drug/factor

Causing interaction

And

Object drug

Affected drug

- Drug – Drug
- Drug – food
- Drug- chemical
- Drug – herbal

Approach to the interactions???

Factors predisposing to Potential drug interactions

- Multiple drug therapy
- Multiple prescribers
- Elderly
- Predisposing illness
- Pharmacogenomic variations

Lexi-Interact™ Online

Interaction Monograph Field Information

Title: Designates the agents or agent groups (categories) involved in the described interaction. The members of an agent category are listed in the Interacting Members section of the monograph.

Risk Rating: Rapid indicator regarding how to respond to the interaction data. Each Interact monograph is assigned a risk rating of A, B, C, D, or X. The progression from A to X is accompanied by increased urgency for responding to the data. In general, A and B monographs are of academic, but not clinical concern. Monographs rated C, D, or X always require the user's attention. The text of the Patient Management section of the monographs will provide assistance regarding the types of actions that could be taken. The definition of each risk rating is as follows:

Risk Rating	Action	Description
A	*No Known Interaction*	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents
B	*No Action Needed*	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.
C	*Monitor Therapy*	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	*Consider Therapy Modification*	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.

X	*Avoid Combination*	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

Summary: A statement qualifying the nature of the interaction(s) detailed in the monograph. This statement may be followed by an indication of outcome severity and/or onset for an unmanaged interaction. Severity indicators include: Minor (effects would be considered tolerable in most cases □ no need for medical intervention); Moderate (medical intervention needed to treat effects; effects do not meet criteria for Major); and Major (effects may result in death, hospitalization, permanent injury, or therapeutic failure. Onset indicators describe the anticipated elapsed time from therapy initiation to adverse event, and include: Immediate (0 □ 12 hours); Rapid (12 □ 72 hours); and Delayed (More than 72 hours); A Yes/No indication regarding whether or not agent administration sequence is important may be included as well. The Reliability Rating provides an indication regarding the volume and nature of reports used to create the interaction monograph. Ratings include EXCELLENT (multiple RCTs; OR single RCT plus >2 case reports), GOOD (single RCT plus < 2 case reports), FAIR (> 2 case reports; OR < 2 case reports plus other supporting data; OR a theoretical interaction based on known pharmacology), and POOR (< 2 case reports with no other supporting data). NOTE: RCT = randomized, controlled clinical trial; OR controlled, multi-patient pharmacokinetic study.

Patient Management: Recommended action steps for preventing adverse outcomes resulting from an anticipated drug interaction. Note: a patient-specific risk:benefit assessment must always be employed.

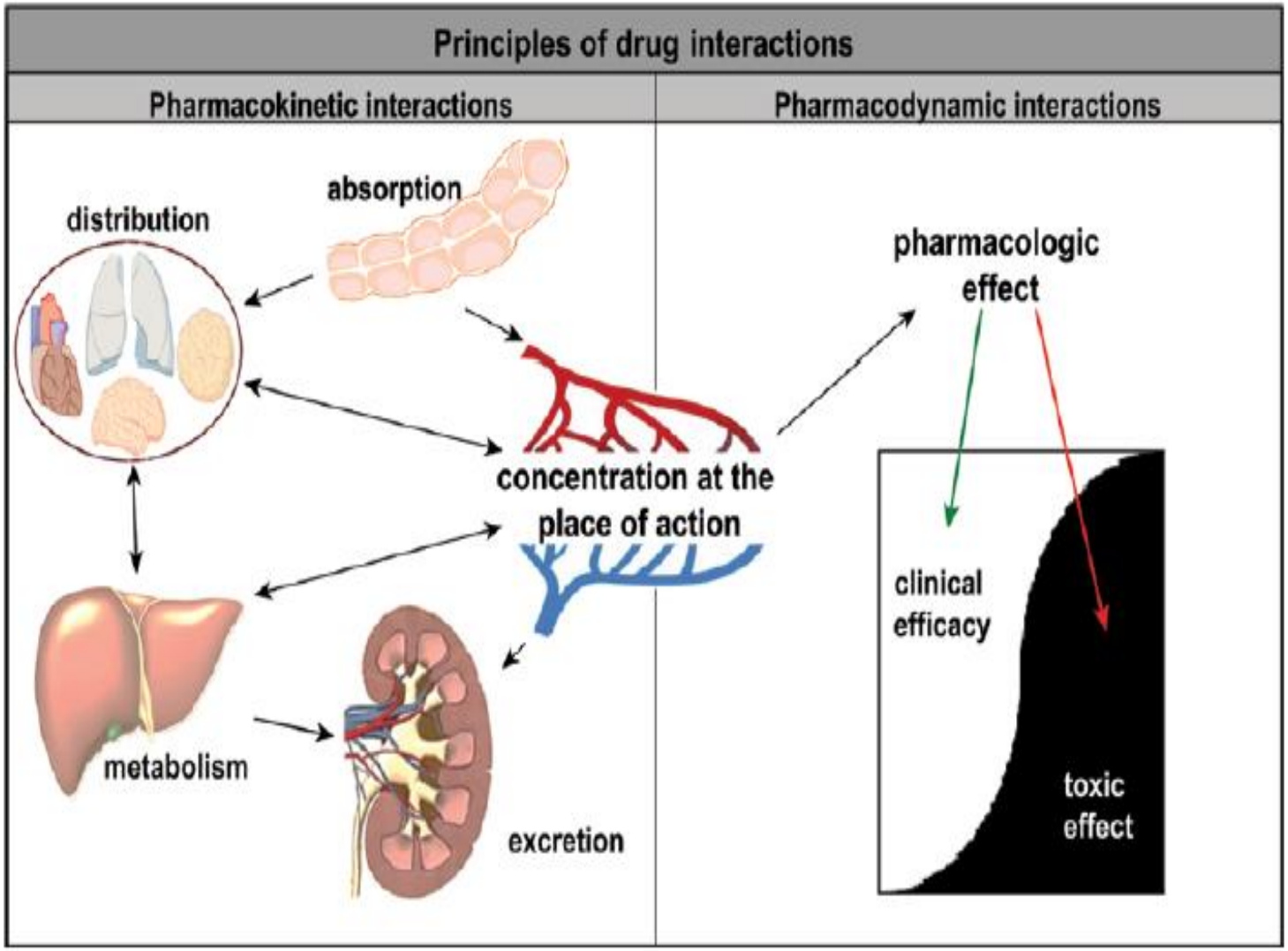
Interacting Category Members: A listing of the agents contained within a specified interacting category. Agents marked with an □*□ have been specifically identified in the published reports described in the Discussion section. Non-interacting category members are noted as □Exceptions□.

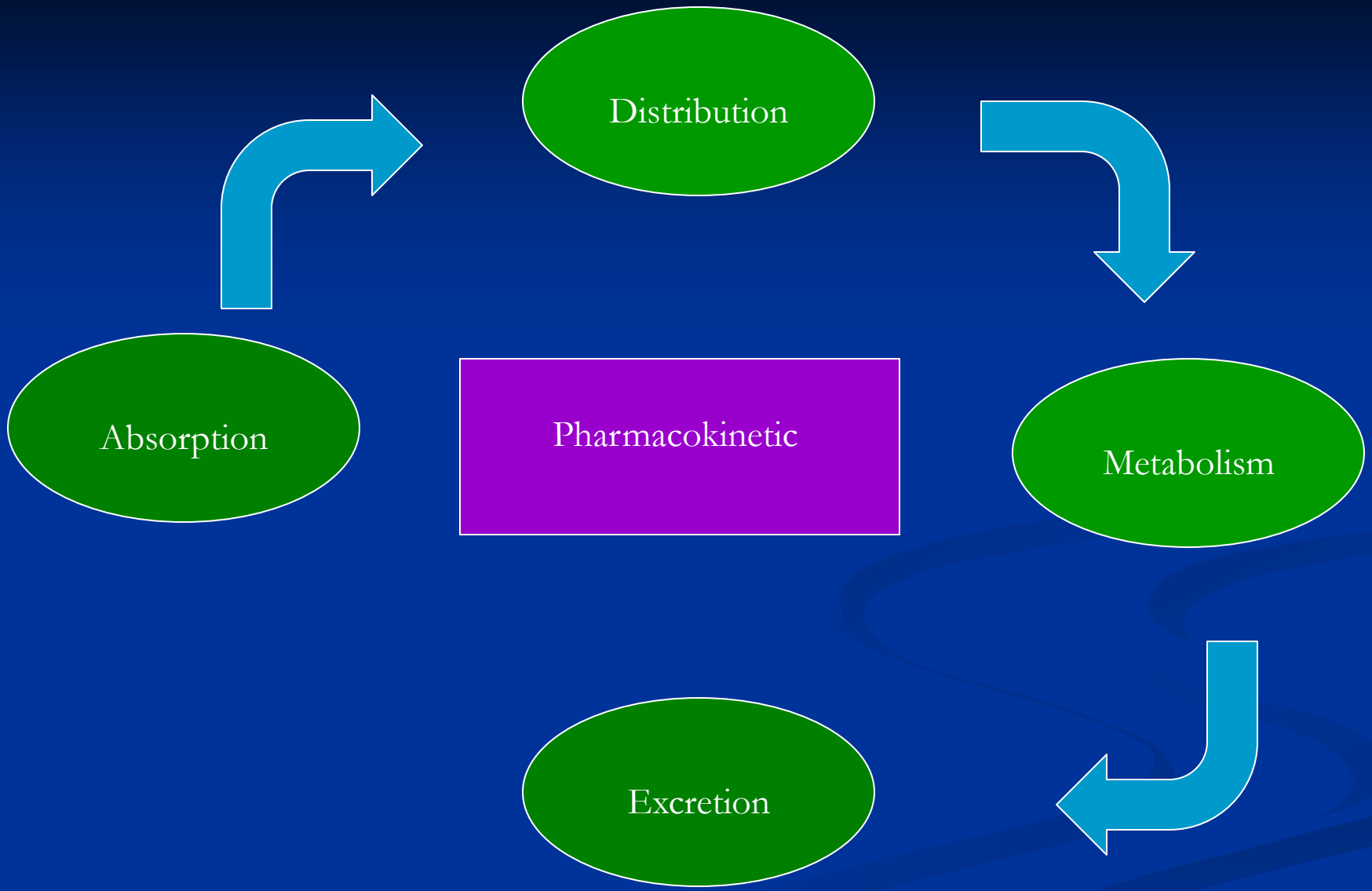
Discussion: A brief presentation of published data pertaining to the observed/presumed interaction.

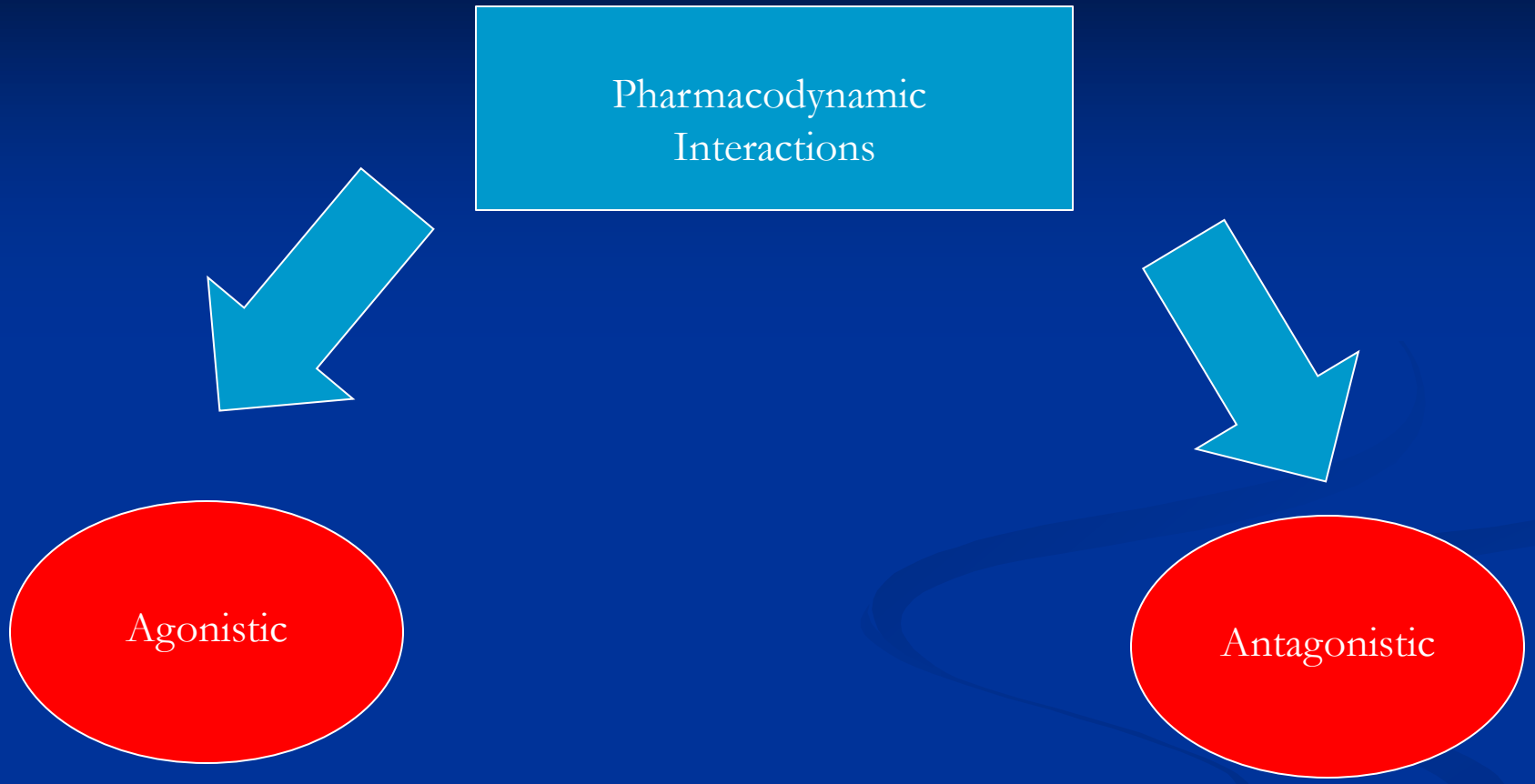
Footnotes: Complete medical literature citations for the data contained in the Discussion section.

Classification by mechanism

- Pharmacokinetic interactions
- Pharmacodynamic interactions


Principles of drug interactions
Pharmacokinetic interactions
Pharmacodynamic interactions
absorption
distribution
pharmacologic effect
concentration at the place of action
clinical efficacy
toxic effect
metabolism
excretion


Distribution
Absorption
Pharmacokinetic
Metabolism
Excretion


Pharmacodynamic Interactions
Agonistic
Antagonistic

Absorption

- Affect in rate or extent of absorption from absorption site
- Most common in GI

Case

A 56 years woman with diagnosis of T2DM. She is under treatment of glyburide 5 md/d for 1 year and during this period she mention regarding only two episode of mild hypoglycemia. During two days ago she bought MOM just before meals for relief of constipation. This morning she is attended in the ER because of a hypoglycemia episode. She deny any increase in glyburide dose/ forgetting meal consumption after glyburide intake.

Attention

- Magnesium salts, which are common ingredients of several over-the-counter medicines (antacids), increase the risk of hypoglycemia by increasing the intestinal absorption rate of SUs. Therefore, SUs should be administered at least 1 hour prior to MOM intake.
- The opposite effect, a decreased intestinal absorption rate, can be expected when cholestyramin is taken concomitantly to SUs

- Acarbose may decrease the serum concentration of digoxin
- Anticholinergics increase the oral bioavailability of metformin by altering GI motility. Thus metformin should be used with caution in combination with anticholinergics
- Metformin use is associated with anemia and vitamin B12 malabsorption, which may be due to a metformin mediated effect on small bowel motility and thus decreased vitamin B12 absorption


5
mcg
Byetta
Each prefilled pen will deliver 60 subcutaneous doses, 5 mcg per dose


VICTOZA

- Alteration in GI absorption

Exenatide & Liraglutide

- Because of the slower gastric emptying, these agents may alter the extent and rate of absorption of concomitantly administered oral medications
- GLP 1 agonists should be used with caution in patients receiving oral medications that have a *narrow therapeutic index* or *require rapid gastrointestinal absorption*

Distribution

- Plasma protein binding

Case

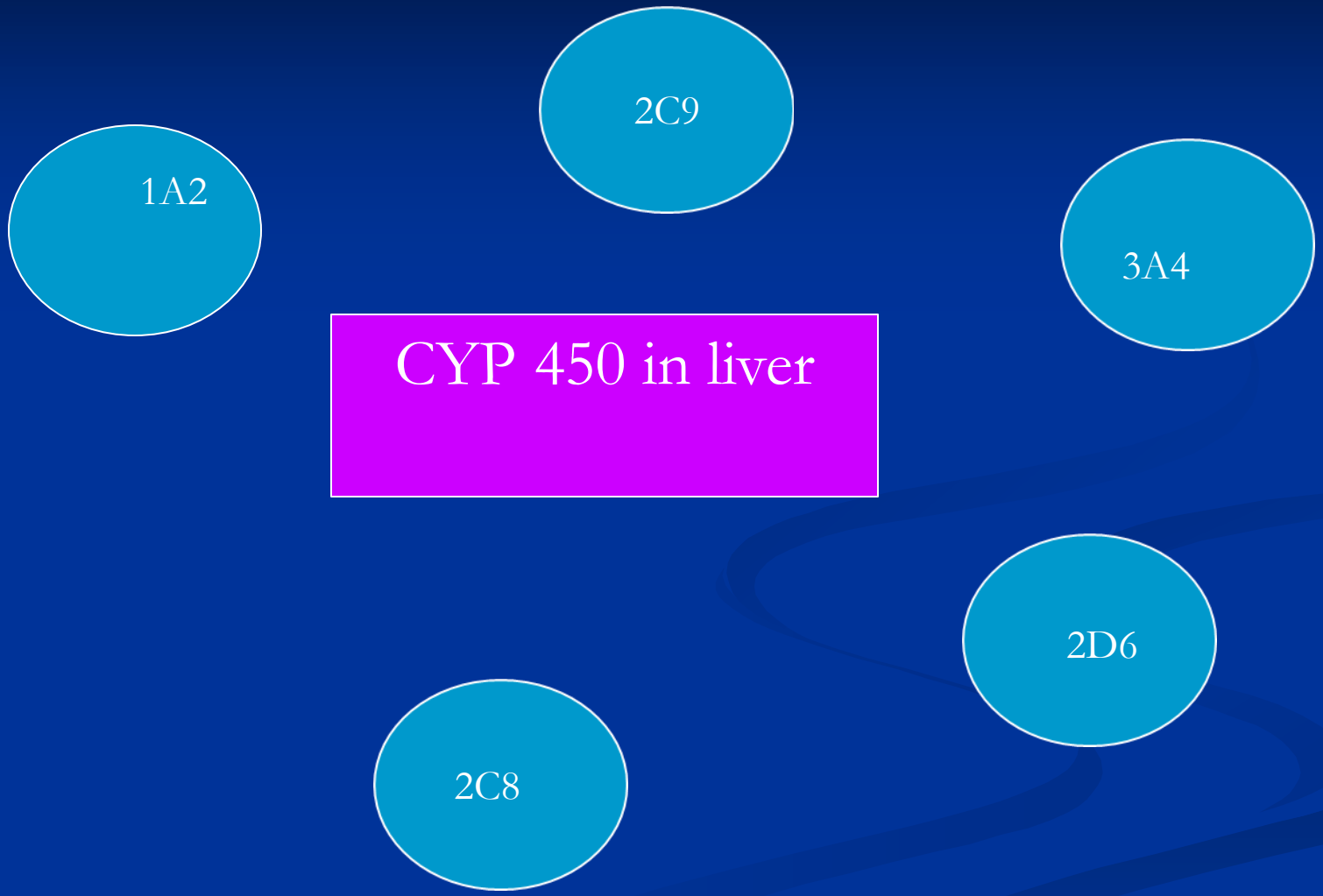
- A 50 years old man on warfarin 5 mg/d for 1 year. Now, INR & PT are in normal range without any signs of bleeding.
- After Diagnosis of DM 2 Endocrinologist administer Glibenclamide 5 mg/d
- After 2 days patients referred to the hospital with ptechiae and epistaxis and raised PT, INR.

High protein binding drugs

- Warfarin
- ASA
- NSAIDs
- Sulfonamides
- Sulfonylurea
- SGLT-2 inhibitors
- Phenytoin
- Valproic acid

- All SGLT-2 inh exhibit high Pr binding. However, clinically significant interactions due to displacement from plasma Pr binding have not so far been described.

Metabolism


2C9
1A2
3A4
CYP 450 in liver
2D6
2C8

Enzyme induction in liver

- Some drug inducers:

Phenytoin, Phenobarbital, Carbamazepine, Rifampin

Enzyme inhibition in liver

- Some drug inhibitors:

Cimetidine, Erythromycin, Itraconazole

- A 52 years woman with diagnosis of DM 2 on metformin 1500 mg/d plus repaglinide 2 mg/d . After diagnosis of a fungal infection physician prescribed Itraconazole 100 mg/d. After 3 days she experience a hypoglycemic episode for first time.

- Inhibition of repaglinide metabolism via 2C8, 3A4 by Itraconazole

TZDs

- Pioglitazone via 3A4 & 2C8
- Rosiglitazone via 2D6 & 2C8

- Rifampin decrease plasma level
- Gemfibrozil & Erythromycin increase plasma level
- When gemfibrozil, a potent CYP2C8 inhibitor, is co-administered, the daily dose of a TZD should be halved due to impaired TZD metabolism


Januvia
MSD


Trajenta®
5 mg
film-coated tablets
Linagliptin
Oral use
30 film-coated tablets
Boehringer Ingelheim


onglyza
5 mg
Saxagliptin
Filmtabletten/ film-coated tablets
28 Filmtabletten/film-coated tablets
Bristol-Myers Squibb / AstraZeneca EEIG

DPP-4 inhibitors

- With the exception of saxagliptin, which is metabolized by 3A4 no clinically relevant drug interaction are known for DPP-4 inhibitors
- The metabolism of Saxagliptin is mediated by CYP3A4/5 and is affected by both inducers and inhibitors of these enzymes (Specifically Rifampin)
- Strong inhibitors of CYP3A4/5, (ketoconazole) moderate inhibitor of CYP3A4/5(Diltiazem) significantly increased saxagliptin level ,probable with other moderate inhibitors (e.g erythromycin, fluconazole and verapamil)
- Linagliptin: inhibitor of CYP3A4 (mainly biliary excreted)

SGLT-2 inhibitors

- They are metabolized in the liver by glucoronidation without involvement of CYP enzymes.


100 F.C.Tablets
Metformin-Najo 500
Metformin
Each F.C. tablet contains:
Metformin HCl 500mg
Take the tablets with or after meals.
Store below 30c and protect from moisture and light.
Keep out of the reach of children.
Iran Najo Pharmaceutical Co.Tehran-Iran
Iran Najo
Batch No:
Mfg.Date:
Exp.Date:
۱۰۰ قرص روکشدار
متفورمین - ناژو ۵۰۰
متفورمین
هر قرص روکشدار حاوی:
۵۰۰ میلی گرم متفورمین هیدروکلراید
دارو را همراه و یا بعد از غذا طبق دستور پزشک میل نمائید.
دارو را دور از نور و رطوبت، در دمای زیر ۳۰ درجه سانتیگراد
و درون جعبه نگهداری کنید.
دارو را دور از دسترس اطفال قرار دهید.


Scanlux® 370 mg/vial
SANOFI

Interactions in Renal clearance

Metformin & Iodinated contrast media

- Mechanism
- literature search identified several cases of lactic acidosis after the use of contrast media in patients taking metformin.
- The manufacturers of metformin say that it should be stopped 48 hours before, or at the time of giving the contrast media and not restarted until 48 hours later, and then only after renal function has been re-checked and found to be normal

2. McCartney MM, Gilbert FJ, Murchison LE, Pearson D, McHardy K, Murray AD. Metformin and contrast media – a dangerous combination? *Clin Radiol* (1999) 54, 29–33.

Pharmacodynamic Interactions

- Alteration of pharmacodynamic effect of a drug

- Antagonistic
- Synergistic/Additive effect

- Increase hypoglycemic effect of Insulin/SU with: Fluroquinolones, Flouxetine, Fibrates, Salicylates

- Decrese hypoglycemic effect of Insulin/SU with: Diuretics, Corticosteroids, Atypical antipsychotics

Quinolones seem to have an insulinotropic effect by increasing the release of insulin via a blockade of ATP-sensitive K channels in a dose dependent manner

- Fluoroquinolones like levoflaxacin, ciprofloxacin, or moxifloxacin should be used with caution in patients with diabetes.

- Thiazide diuretics impair antidiabetic drug efficacy by increasing insulin resistance and increasing plasma glucose concentrations due to reduced total body potassium.
- A recent study identified thiazide diuretics

as the agents with the most frequent drug–drug interaction with antidiabetic medication

Drug – food Interactions

- Change in Bioavailability
- Change in Pharmacodynamic effects of drug

Administartion of Antidiabetic agents regarding food

Group	recommendation
Metformin	With meal
Sulfonylurea	30 min prior meal
Glinides	Just before meal
Glitazones	May be administered without regard to meals
α glucosidase Inh	With meal
DPP-4 Inh	May be taken with or without food
SGLT-2 Inh	May be taken with or without food

Change in pharmacodynamic

- Alcohol with SU/Insulin/ Glinides
- Ethanol consumption generally should be restricted because can alter glucose tolerance and insulin secretion and there is additive hypoglycemic effect.
- Alcohol with metformin

Table 1. Relevant herb-drug interactions with commonly prescribed antidiabetic drugs [Holstein *et al.*, 2012, Rehman *et al.*, 2014].

Interacting herb	Pharmacokinetic mechanism; pharmacodynamic mechanism	Antidiabetic drug affected
Aloe vera	inhibitory effects on CYP3A4 and CYP2D6; insulin-sensitizing effects	increased efficacy: Pioglitazone and Repaglinide; additive effects with antidiabetics in general
Andrographis paniculata	inhibitory effects on CYP3A4 and CYP2C9 activities; enhanced glucose transport by glucose transporter 4	probably increased efficacy: Glibenclamide, Glimepiride, Nateglinide, Rosiglitazone; Pioglitazone, and Repaglinide; maybe additive effects with antidiabetics in general
Ginseng	induction of CYP3A4; stimulates insulin secretion	probably decreased efficacy: Glibenclamide; Pioglitazone; Meglitinides; Sitagliptin, Saxagliptin; additive effects with antidiabetics
Karela *(Momordica charantia)*	inhibition of CYP2C9; stimulates insulin secretion	probably increased efficacy: Glibenclamide, glimepiride, nateglinide, and Rosiglitazone; additive effects with antidiabetics in general
Lycium	inhibition of CYP2C9; improved glucose transport and insulin signaling	slightly increased efficacy (maybe): Glibenclamide, Glimepiride, Nateglinide, and Rosiglitazone; maybe additive effects with antidiabetics in general
St John's Wort	induction of CYP3A4, 1A2, 2D6, 2E1; drug transporter: p-glycoprotein induced	decreased efficacy. Sulfonylurea; Thiazolidinediones; Meglitinides; Sitagliptin (probably), Saxagliptin (probably)
Herbs with Glucosamines	increased insulin resistance	may diminish antidiabetic efficacy
Herbs with Isoflavones	inhibitory effects on CYP2C9 and CYP3A4	probably increased efficacy: Glibenclamide, Glimepiride, Nateglinide, Rosiglitazone; Pioglitazone, and Repaglinide
Herbs with Levocarnitine	increased glucose oxidation	additive effects with antidiabetics in general

- GLP-1 analogues & SGLT-2 inh possess a very low interaction potential and seem to be ideal combonation partners in diabetes therapy.

- Diabetic patients should be strictly advised not to take any herbal drug preparation concomitantly with antidiabetic medication, without previously consulting their diabetologist/pharmacist

THE END