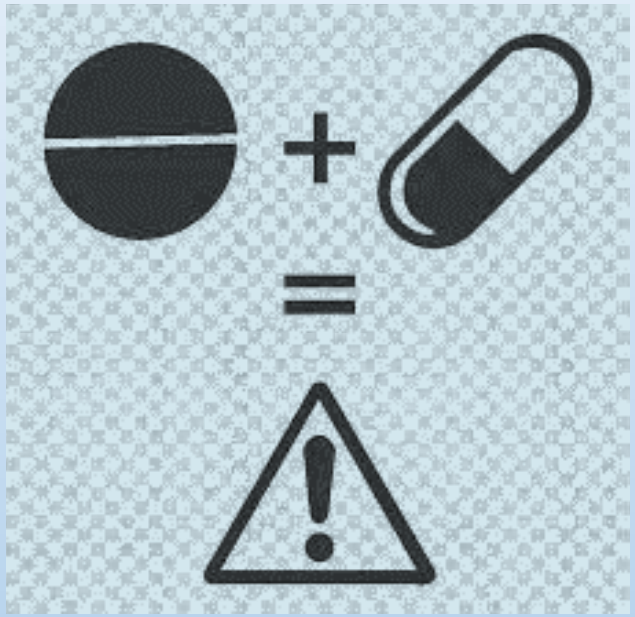
Focus on some major DDI; a case-based approach



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December 15 , 2020

DDI in Smokers!

- A 36 Y/O male admitted to hospital with **akathisia and parkinsonism**
- **PMH**: Schizophrenia and MDD from 2 yrs ago,
- **Current Drug**: Olanzapine (30 mg/day) and sertraline (100 mg/day)
- **HH**: smoking about 1 pack (20 cigarettes) of cigarettes from 1 years ago
- Two weeks ago, patient decided to stop smoking and quit it one week ago, completely
- Now (1 weeks after complete cessation of smoking), pt admitted with akathisia and parkinsonism.

Smoking and drugs interaction

- Tobacco smoke (>1 week of more than 6-7 cigarettes?) contains PAHs that induce 1A2, 2E1 (Alcohol), UDP-glucuronosyltransferases
- Determined by the number and type of cigarettes smoked and the degree of smoking
- Mainly Psych drugs
- Induction and recovery after 7 days and 4-7 days of initiation of smoking, respectively.
- Generally seen at > 7 cigarettes/day but the process is complicated and effects are difficult to predict

- CYP 1A2 Substrates: Olanzapine (▲Cl up up to 98%), Clozapine (▼ level up to 50%), Caffeine (▲Cl to 99%), Theophylline (▲Cl 58-100%) , Fluvoxamine, Alprazolam, Warfarin (R-enantiomer, monitor INR), Clopidogrel, ▼ SC inslulin (due to peripheral vasoconstriction and▼ absorption), TCA (may need dose modification)

- PD interaction: BDZ (▲ sedation), BBs (need higher dose due to nicotine-mediated sympathetic activation), OCP (▲ stroke risk esp. >15 cigarettes/d and >35 y/o), Opioid (need higher dose, Unknown mechanism)

Psych drugs;
Maudsley 13ed

Table 11.5 Psychotropic drugs affected by smoking status

Drug	Effect of smoking	Action to be taken on stopping smoking	Action to be taken on re-starting
Agomelatine[3]	Plasma levels reduced	Monitor closely Dose may need to be reduced	Consider re-introducing previous smoking dose
Benzodiazapines[2,4]	Plasma levels reduced by 0–50% (depends on drug and smoking status)	Monitor closely. Consider reducing dose by up to 25% over 1 week	Monitor closely. Consider re-starting 'normal' smoking dose
Carbamazepine[2]	Unclear, but smoking may reduce carbamazepine plasma levels to a small extent	Monitor for changes in severity of adverse effects	Monitor plasma levels
Chlorpromazine[2,4,5]	Plasma levels reduced. Varied estimates of exact effect	Monitor closely, consider dose reduction	Monitor closely, consider re-starting previous smoking dose
Clozapine[6–11]	Reduces plasma levels by up to 50% Plasma level reduction may be greater in those receiving valproate	Take plasma level before stopping. On stopping, reduce dose gradually (over 1 week) until around 75% of original dose reached (i.e. reduce by 25%). Repeat plasma level 1 week after stopping. Anticipate further dose reductions	Take plasma level before re-starting. Increase dose to previous smoking dose over 1 week. Repeat plasma level

Drug	Effect of smoking	Action to be taken on stopping smoking	Action to be taken on re-starting
Duloxetine[12]	Plasma levels may be reduced by up to 50%	Monitor closely Dose may need to be reduced	Consider re-introducing previous smoking dose
Fluphenazine[13]	Reduces plasma levels by up to 50%	On stopping, reduce dose by 25%. Monitor carefully over following 4–8 weeks. Consider further dose reductions	On re-starting, increase dose to previous smoking dose
Fluvoxamine[14]	Plasma levels decreased by around a third	Monitor closely Dose may need to be reduced	Dose may need to be increased to previous level
Haloperidol[15,16]	Reduces plasma levels by around 25–50%	Reduce dose by around 25%. Monitor carefully. Consider further dose reductions	On re-starting, increase dose to previous smoking dose
Loxapine[17] (inhaled)	Half-life reduced from 15.7 h to 13.6 h	Monitor	Monitor
Mirtazapine[18]	Unclear, but effect probably minimal	Monitor	Monitor
Olanzapine[11,19–22]	Reduces plasma levels by up to 50%	Take plasma level before stopping. On stopping, reduce dose by 25%. After 1 week, repeat plasma level. Consider further dose reductions	Take plasma level before restarting. Increase dose to previous smoking dose over 1 week. Repeat plasma level
Trazodone[23]	Around 25% reduction	Monitor for increased sedation. Consider dose reduction	Monitor closely. Consider increasing dose
Tricyclic antidepressants[2,4]	Plasma levels reduced by 25–50%	Monitor closely. Consider reducing dose by 10–25% over 1 week. Consider further dose reductions	Monitor closely. Consider re-starting previous smoking dose

Smoking and drugs interaction

- Monitor closely :TDM (after 4-7 days of ▲or ▼ smoking), efficacy (when ▲ cigarettes) and side effects (when ▼ smoking) especially after 4th day of smoking cessation.
- Some suggested dosage-correction factor of 1.5 for clozapine and olanzapine in smokers
- Dose modification is required based on clinical situation

- **Back to case:** EPS symptoms improved within 5 days following a reduction in his olanzapine dose to 20 mg daily

UST: false + or -

- A 27 Y/O female
- UST showed positive result for methadone!
- PMH: Hypothyroidism, GERD, insomnia.
- DH: Levothyroxine 100 mcg OD. Diphenhydramine 50 mg TDS (from 1 week ago), Famotidine 20 mg QHS, Trazodone 25 mg QHS, Pantoprazole 40 mg OD.
- Patient refused the use of any opioid or opioid likes substances.
- False or True test?

- 2 main types of UDTs: Screening and confirmatory tests
- Screen test are performed using immunoassay
- Immunoassays use antibodies to detect the presence of drug metabolites or classes of drug metabolites in the urine.
- Immunoassays detect substances with similar characteristics, resulting in cross-reactivity leading to false positive results
- Confirmatory test: Gas chromatography/mass spectrometry (GC-MS), identify specific molecular structure.

Commonly Ordered Drug Tests, Windows of Detection, and Analytes

Test	Window of detection[11-14]	Analytes[13,15,16]
Amphetamines	2 to 3 days	Amphetamine, methamphetamine, methylenedioxyamphetamine, methylenedioxymethamphetamine
Benzodiazepines*		Alpha-hydroxyalprazolam, 7-aminoclonazepam, oxazepam
Short acting	3 to 5 days	
Long acting	Up to 30 days	
Buprenorphine	Up to 11 days	Norbuprenorphine
Cannabis		11-nor-9-carboxy-tetrahydrocannabinol
Single use	2 days	
3 times per week	2 weeks	
Daily use	2 to 4 weeks	
Very heavy use	4 to 6 weeks (up to 12 weeks)	
Cocaine	1 to 5 hours (2 to 4 days for metabolites)	Benzoylecgonine, ecgonine methyl ester
Codeine	1 to 2 days	Hydromorphone, morphine
Fentanyl	2 to 3 days	Norfentanyl
Heroin and morphine	3 days	Codeine, hydromorphone, 6-monoacetylmorphine, morphine
Hydromorphone (Dilaudid)	1 to 2 days	Hydromorphone
Methadone	3 to 4 days (up to 14 days)	2-ethylidene-1,5-dimethyl-3, 3-diphenylpyrrolidine
Oxycodone		Noroxycodone, noroxymorphone, oxycodone, oxymorphone
Immediate release	1 to 1.5 days	
Controlled release	1.5 to 3 days	
Oxymorphone		Noroxymorphone, oxymorphone
Immediate release	1.5 to 2.5 days	
Controlled release	1 to 4 days	
Phencyclidine	1.5 to 10 days	Phencyclidine
Tapentadol (Nucynta)	1 to 5 days	Tapentadol, tapentadol O-sulfate
Tramadol	2 to 4 days	Nortramadol
Zolpidem (Ambien)	1 to 5 days	Zolpidem

Medication	AMP/MET	BAR	BZO	THC	LSD	MTD	OPI	PCP	TCA
Amitriptyline					X				
Bupropion	X				X				
Buspirone					X				
Carbamazepine									X
Cyclobenzaprine									X
Dextromethorphan							X	X	
Diltiazem					X				
Diphenhydramine						X		X	
Doxylamine						X	X	X	
Fentanyl					X				
Fluoxetine	X				X				
Ibuprofen		X		X				X	
Labetalol	X				X				
Lamotrigine								X	
Metformin	X								
Methylphenidate	X				X				
Metoclopramide					X				
Naproxen		X		X					
Prochlorperazine					X				
Promethazine	X								
Pseudoephedrine	X								
Quetiapine						X			X
Quinolones[a]							X		
Ranitidine	X								
Risperidone					X				
Sertraline			X		X				
Tramadol								X	
Trazodone	X				X				
Venlafaxine								X	
Verapamil					X	X			

TABLE 3

Common Medications That Can Cause False-Positive Results on Urine Drug Testing

Drug	Cross-reactive medications/substances
Amphetamines	Amantadine, benzphetamine (Regimex), bupropion (Wellbutrin), chlorpromazine, clobenzorex (not available in the United States), desipramine, dextroamphetamine, ephedrine (Akovaz), fenproporex (not available in the United States), isometheptene (component of Prodrin), labetalol, levomethamphetamine (active ingredient in some over-the-counter nasal decongestant inhalers), methamphetamine, 3,4-methylene-dioxymethamphetamine (MDMA), methylphenidate (Ritalin), phentermine (Adipex-P), phenylephrine, promethazine, pseudoephedrine, ranitidine (Zantac), selegiline (Elde-pryl), thioridazine, trazodone, trimethobenzamide (Tigan), trimipramine (Surmontil)
Benzodiazepines	Oxaprozin (Daypro), sertraline (Zoloft)
Cannabinoids	Dronabinol (Marinol), efavirenz (Sustiva), hemp-containing foods, proton pump inhibitors, tolmetin and other nonsteroidal anti-inflammatory drugs
Cocaine	Coca leaf tea, topical anesthetics containing cocaine
Opioids	Dextromethorphan, heroin, quinine, quinolones, rifampin, verapamil
Phencyclidine	Dextromethorphan, diphenhydramine (Benadryl), doxylamine, ibuprofen, ketamine (Ketalar), meperidine (Demerol), thioridazine, tramadol, venlafaxine

Adapted with permission from Smith MP, Bluth MH. Common interferences in drug testing. Clin Lab Med. *2016;36(4): 665-666.*

Opioids

- Many methadone immunoassays detect only the parent compound. A few medications, including verapamil, diphenhydramine, and doxylamine, have been reported to cause false-positive screens for methadone

Opioids/opiates/heroin[17,18,74-90]	Dextromethorphan Diphenhydramine[e] Doxylamine[e] Heroin Opiates (codeine, hydromorphone, hydrocodone, morphine) Poppy seeds
	Quinine Quinolones Rifampin Verapamil and metabolites[e]

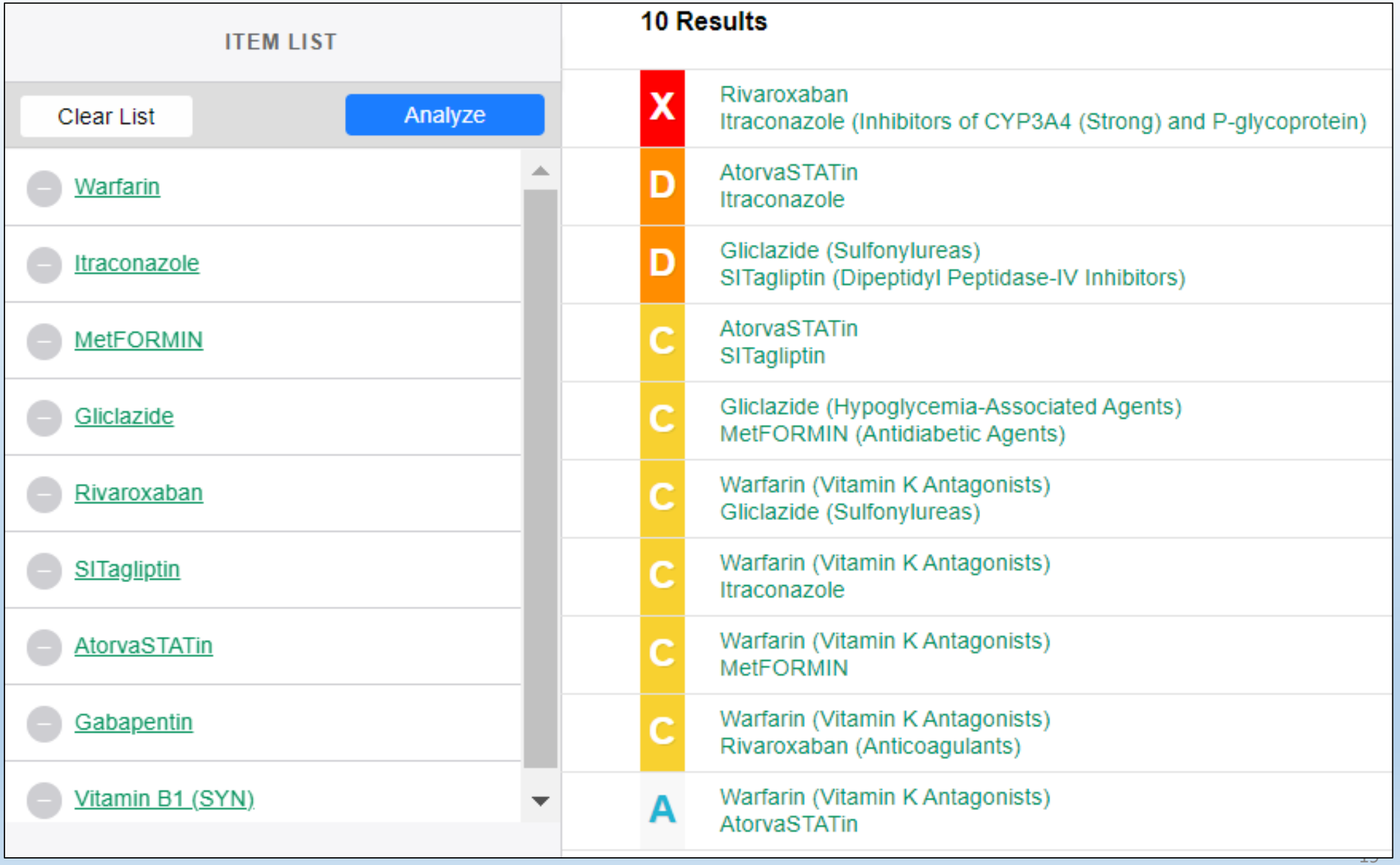
Back to case:

- Diphenhydramine discontinued for a few days.
- Repeated UST showed negative result for methadone

- Trazodone may cause false + for LSD and AMP/MET not OPI of MET

DOACs Interactions!

- 56 Y/O male
- Drugs list: Symbicort 320 two puff BD, Itraconazole 200 BD, Metformin 1000 BD, Gliclazide MR 30 mg daily, Sitagliptin 50 mg daily, Atorvastatin 10 mg daily, Gabapentin 300 mg QHS, Vitamin B1 300 daily.
- DVT was diagnosed from 2 days ago.
- Rivaroxaban 15 mg PO BD for 3 weeks (form 2 days ago) and then 20 mg OD.
- Are there any DDIs? Does the patient eligible for DOACs?


ITEM LIST
Clear List
Analyze
Warfarin
Itraconazole
MetFORMIN
Gliclazide
Rivaroxaban
SITagliptin
AtorvaSTATin
Gabapentin
Vitamin B1 (SYN)
10 Results
X
Rivaroxaban
Itraconazole (Inhibitors of CYP3A4 (Strong) and P-glycoprotein)
D
AtorvaSTATin
Itraconazole
D
Gliclazide (Sulfonylureas)
SITagliptin (Dipeptidyl Peptidase-IV Inhibitors)
C
AtorvaSTATin
SITagliptin
C
Gliclazide (Hypoglycemia-Associated Agents)
MetFORMIN (Antidiabetic Agents)
C
Warfarin (Vitamin K Antagonists)
Gliclazide (Sulfonylureas)
C
Warfarin (Vitamin K Antagonists)
Itraconazole
C
Warfarin (Vitamin K Antagonists)
MetFORMIN
C
Warfarin (Vitamin K Antagonists)
Rivaroxaban (Anticoagulants)
A
Warfarin (Vitamin K Antagonists)
AtorvaSTATin

Characteristics	Thrombin inhibitor	Factor Xa inhibitors		
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Prodrug	Yes	No	No	No
Bioavailability	3–7%	50%	62%	80%
Time to peak concentration h	1–3	1–3	1–3	2–4
Half-life h	12–17	8–15	8–10	7–13
Renal clearance	80%	25%	35%	66%
Metabolism	P-glycoprotein	P-glycoprotein, CYP3A4	P-glycoprotein, CYP3A4	P-glycoprotein, CYP3A4

- All of them are substrate for P-gp (which involved in Gut and renal Cl)
- CYP3A4 involved in the hepatic clearance of rivaroxaban and apixaban.
- Generally, DOAC use is not recommended in combination with **strong inducer** (such as Phenytoin, CBZ, RIF, etc.) and **inhibitors** of both CYP3A4 and P-gp
- Dose modification may be required in some combination (such as Amiodarone) and in some patients (such as CKD)

Amiodarone	Apixaban	Combination is considered safe
	Betrixaban	Reduce dose of betrixaban to 80 mg once then 40 mg daily; avoid use if CrCl <30 ml/min
	Dabigatran	Combination considered safe if CrCl >50 ml/min Avoid combination if CrCl <50 ml/min for VTE and <30 ml/min for NVAF
	Edoxaban	Combination is considered safe
	Rivaroxaban	Avoid use if CrCl <80 ml/min
Calcium-Channel Blockers		
Verapamil	Apixaban	Combination is considered safe
	Betrixaban	Reduce dose of betrixaban to 80 mg once then 40 mg daily; avoid use if CrCl <30 ml/min
	Dabigatran	Avoid use if CrCl <30 ml/min for NVAF and <50 ml/min for VTE
	Edoxaban	Combination is considered safe
	Rivaroxaban	Avoid combination when CrCl is <80 ml/min
Diltiazem	Apixaban	Combination is considered safe
	Betrixaban	Reduce dose of betrixaban to 80 mg once, then 40 mg daily; avoid use if CrCl <30 ml/min
	Dabigatran	Combination is considered safe
	Edoxaban	Combination is considered safe
	Rivaroxaban	Avoid use if CrCl <80 ml/min
Enzyme Inducers		
Phenytoin, carbamazepine, primidone, rifampin, phenobarbital, St. John's wart	Apixaban	Avoid combination; consider warfarin
	Betrixaban	
	Edoxaban	
	Dabigatran	
	Rivaroxaban	

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Clarithromycin; Erythromycin	Moderate P-gp competition and strong CYP3A4 inhibition	+15 to 20%	+60% AUC +30% C_{max}	+90%[SmPC]	+34% (Erythromycin)/ +54% (Clarithromycin) [SmPC129]
Rifampicin	P-gp/BCRP and CYP3A4/ CYP2J2 inducers	Minus 66%[SmPC]	Minus 54%[138]	Minus 35%, but with compensatory increase of active metabolites	Up to minus 50%[SmPc]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[129]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[SmPC]
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150% (US: 2 × 75 mg if CrCl 30–50 mL/min)	+100%[136]	+87 to 95%[132] (reduce NOAC dose by 50%)	Up to +160%[SmPc]
Posaconasole	Mild to moderate P-gp inhibition	SmPC	SmPC		SmPC
Naproxen	P-gp competition; pharmacodynamically increased bleeding time	No data yet	+55%[139]	No effect	No data yet
H2B; PPI; Al-mg-hydroxide	GI absorption	Minus 12–30%	No effect	No effect[SmPc]	No effect[140]
St. John's wort	P-gp/BCRP and CYP3A4/ CYP2J2 inducers				

The hatched colour coding indicates no clinical or PK data available, and recommendations are based on the respective NOAC SmPC (where available) or expert opinion. Some of the colour codes will likely require adaptation as more data become available over time.

White: No relevant drug–drug interaction anticipated.

Yellow (light): Caution is needed in case of polypharmacy or in the presence of ≥2 bleeding risk factors.

Yellow: Consider dose adjustment or different NOAC if 2 or more 'yellow' factors are present (see *Figure 3*).

Orange: Consider dose adjustment or different NOAC (see *Figure 3*).

Red: contraindicated/not recommended.

Brown (dark): Contraindicated due to *reduced* NOAC plasma levels.

Brown (light): Use with caution or avoid. Either expert opinion or the NOAC label mentions that co-administration is possible despite a decreased plasma level, which is deemed not clinically relevant (nevertheless, since not tested prospectively, such concomitant use should be used with caution, and avoided when possible).

Where no data or SmPC instructions were available, expert opinion was based on the following principles:

Where no data or SmPC instructions were available, expert opinion was based on the following principles:

- Strong CYP3A4 and/or P-gp inducer—should not be used (dark brown).
- Moderate CYP3A4 or P-gp inducer—use with caution or avoid (light brown).
- Strong CYP3A4 and/or inhibitor—should not be used (red).
- Moderate CYP3A4 or P-gp inhibitor—use with caution, consider dose reduction or different NOAC (orange).
- Mild CYP3A4 and/or P-gp inducers or inhibitors—caution is needed with polypharmacy or in the presence of ≥2 bleeding risk factors (yellow).

Back to case:

- Itraconazole is a potent inhibitor of P-glycoprotein and CYP3A4
- Alternative for itraconazole?! No suitable alternative, routinely.
- Can DOACs be used in this case? Unpredictable DDI. **Not recommended**.
  - 140-150% ▲ Dabigatran level
  - 100 % ▲ Apixaban level
  - Up to 160% ▲ Rivaroxaban level
- Warfarin as an alternative (after 5 days of parenteral AC) ; INR 2-3
- Itraconazole ▲ INR (effect on 2C9 and via other mechanism), monitor INR

OCP DDI

- 34 Y/O female had unprotected intercourse 12 hours ago.
- PMH: GTCs (fro 4 years ago. Last episode was for 4 mo. ago), IDA
- DH: CBZ 200 mg BD, ferrous sulphate 2 tab EOD, Calcium-D daily, vitamin D 50000 weekly.
- Weight 56 kg and Height 162 cm
- **As a pharmacist, what is your recommendation regarding method of EC in this case?**

OCP in Epilepsy:

Enzyme inducing vs non-enzyme inducing AEDs

Enzyme inducing anti-epileptic drugs	Non-enzyme inducing anti-epileptic drugs
***carbamazepine**	Acetazolamide
eslicarbazepine acetate	**clobazam**
oxcarbazepine	clonazepam
phenobarbital	ethosuximide
phenytoin	gabapentin
primidone	lacosamide
rufinamide	**levetiracetam**
****topiramate**	*****Lamotrigine**
perampanel	piracetam
	pregabalin
	sodium valproate
	stiripentol
	tiagabine
	vigabatrin
	zonisamide
	*Commonly used anti-epileptic drugs are in **bold** ** in doses >200mg
	*** Efficacy reduced by combined oral contraceptive drugs

- Most (78.9%) women with epilepsy reported having at least one unintended pregnancy
- Enzyme-inducing AED (carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, eslicarbazepine and topiramate 200mg/d) can result in OCP failure (▼ Es and Ps) through CYP3A4 induction
- Non-enzyme-inducing AEDs (e.g. sodium valproate, levetiracetam, gabapentin, vigabatrin, tiagabine and pregabalin) do not decrease the efficacy of contraceptives

Practical Tips for contraception choice in Epilepsy

- **For woman taking Enzyme inducing**:
  - ✓ LNG-IUD or Cu-IUD or DMPA (q10 week instead of q3 month)
  - ✓ Do not use POP
  - ✓ Use of implants and rings is not recommended.
  - ✓ Use of low (20mcg Es) and standard dose (30-35 mcg Es) of COC is not recommended.
  - ✓ Use HD (50-70 mcg Es) or continuous use of monophasic OCP (without a pill free interval) or tricycling regimen* plus pill-free interval of 4 days is suggested by experts (± barrier)

- **For woman taking non-enzyme-inducing AEDs**: Women on these medications can choose any contraceptive and emergency contraceptive method.

- **Emergency contraception for woman taking Enzyme inducing**:

✓ Cu-IUD is choice.

✓ Double dose of LNG (3mg up to 2 mo. after AED last dose).

✓ Do not use Ella.

✓ Yuzpe is not recommended

Lamotrigine

- ✓ Minimal effects on the efficacy of combined oral contraceptives
- ✓ COC decrease lamotrigine level by 25-70% (>20% fall in level after 3 days).
- ✓ No interaction with POP, EC, LNG-IUD, DMPA and Implants
- **COC + Lamotrigine**: Decrease efficacy during hormone exposure and increase side effects (such as rash) during pill-free days
  - ✓ **Lamotrigine monotherapy**: use of COC is not recommended. Increase the lamotrigine dose and extend the cycle (no pill free interval) is suggested.
  - ✓ **Combination therapy with non-enzyme inducing like sodium valproate**: no dose adjustment but be careful about drug toxicity; limit pill free interval

Back to case; pharmacist advice:

- **Preferred EC for patient on CBZ:**
  - ✓ IUD (consider cost, access, insertion and side effects)
  - ✓ Double dose LNG (3 mg once or 1.5 BD) preferentially at first 72 hours of intercourse
  - ✓ Ella is not recommended
  - ✓ Consult regarding routine use of contraception (like DMPA q 10 week)

Lithium DDI

- 56 Y/O female presented to psych. clinic with 1 week history of nausea, drowsiness and mild tremor
- **PMH** was notable for schizophrenia and bipolar disorder
- **PDH** from 10 years ago was lithium , valproate, quetiapine, and risperidone
- Other : dental pain and Ibuprofen 800 mg PRN TDS from 1 week ago.
- She is on salt restrict diet from 2 weeks ago
- Lithium level for 3 mo. ago= 0.65 mEq/L
- Current Lithium level = 1.3 mEq/L
- **What's explanation for this phenomen?**

❑ Li + NSAIDs:

- ✓ NSAIDs ▲ level of Lithium; it depends on type, dose and duration of NSAID and individual factor (salt intake, kidney function, age)
- ✓ 10-400% ▲ in Li level
- ✓ Mechanism: unknown;
  - NSAIDs inhibit renal PGE2 ▼ RBF▼ the renal excretion of Li
  - NSAIDs inhibit renal PGE2 ▲ reabsorption of sodium and Li
- Usually after 5-7 days (few days to several months)
- Risk factors: impaired renal function, renal artery stenosis or heart failure and who are dehydrated or on a low-salt diet.

❑ Li + NSAIDs:

- Monitor Li level closely every 5 days after imitation of any NSAID
- Patient education regarding symptoms of lithium toxicity and modification of risk factors such as dehydration and salt restriction
- Use of lowest effective dose of NSAID or Acetaminophen
- Use of regular NSAID not PRN
- Be aware about OTC drugs and other interacting medication

Table 2. Sorts of interactions between lithium and different NSAIDs

Well-established interaction (↑ *lithium*)	Celecoxib, diclofenac, flurbiprofen, indomethacin, ketorolac, ketoprofen, lornoxicam, mefenamic acid, meloxicam, niflumic acid, phenylbutazone, piroxicam
Variable interaction (↔ *or* ↑ *or* ↑↑ *lithium*)	Ibuprofen and naproxen
Without proven interaction	Acetylsalicylic acid and sulindac

↔ no change; ↑ slight increase; ↑↑ moderate increase.

Other Li interaction

- ✓ Narrow TI: DDI can precipitate lithium toxicity
- ✓ Most clinically significant interactions are with drugs that alter renal sodium handling

Drug group	Magnitude of effect	Timescale of effect	Additional information
ACE inhibitors	■ Unpredictable ■ Up to 4-fold increases in [Li]	Develops over several weeks	■ 7-fold increased risk of hospitalisation for lithium toxicity in the elderly ■ **Angiotensin II receptor antagonists** may be associated with similar risk
Thiazide diuretics	■ Unpredictable ■ Up to 4-fold increases in [Li]	Usually apparent in first 10 days	■ Loop diuretics are safer ■ Any effect will be apparent in the first month

Drugs That Decrease Lithium Levels

Theophylline, caffeine

Theophylline and caffeine may increase renal clearance of lithium and result in a decrease in levels in the range of 20%.

Acetazolamide

Acetazolamide may impair proximal tubular reabsorption of lithium ions.

Sodium

High dietary sodium intake promotes the renal clearance of lithium.

Back to case;

- D/C PRN ibuprofen
- Regular use of ceiling dose of NSADI (400 mg TDS) and monitor level
- Acetaminophen
- Constant intake of salt intake
- Li level return to 0.8 after D/C of ibuprofen

Supplement and immunosuppressant

- 32 Y/O female ask you as a pharmacist regarding safety of Echinacea for herself
- **PMH**: KTx from 4 years ago
- **PDH**: mycophenolate mofetil (500 mg TDS), TAC (1.5 mg BD) , PDN (5 mg daily), Losartan (25 mg BD), vitamin D (1000 U/day), folic acid (1 mg daily), famotidine (20 mg QHS)
- Laboratory tests were within normal range

Resources for Supplement–Drug Interactions

Resource	*Website*	*Comments*
About Herbs, Botanicals & Other Products	https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs	Dietary supplement monographs and interaction checker from Memorial Sloan Kettering Cancer Center
The Allied and Complementary Medicine Database*	https://www.ebscohost.com/academic/amed-the-allied-and-complementary-medicine-database	Bibliographic records for more than 600 journals dating back to 1995
ConsumerLab.com*	https://www.consumerlab.com/	Quality testing of many dietary supplements
Facts & Comparisons eAnswers*	http://online.factsandcomparisons.com/index.aspx	Drug and dietary supplement monographs
Indiana University Clinical Pharmacology	http://medicine.iupui.edu/clinpharm/ddis/clinical-table	Lists of drugs metabolized by common cytochrome P450 enzymes
Lexi-Natural Products*	http://webstore.lexi.com/Store/Individual-Databases/Lexi-Natural-Products	Software for dietary supplement monographs
Micromedex*	http://micromedex.com/	Drug and dietary supplement monographs with interaction checker
Natural Medicines*	https://naturalmedicines.therapeuticresearch.com/	Dietary supplement database with interaction checker
NIH's National Cancer Institute Office of Cancer Complementary and Alternative Medicine	https://cam.cancer.gov/	Cancer-specific, evidence-based information on many dietary supplements and complementary therapies
NIH's National Center for Complementary and Integrative Health	https://nccih.nih.gov/	Evidence-based information on many complementary therapies
NIH's Office of Dietary Supplements	https://ods.od.nih.gov/	Fact sheets and information on many dietary supplements
NSF International	http://www.nsf.org/services/by-industry/dietary-supplements	Dietary supplement safety information and testing
PubMed	http://www.ncbi.nlm.nih.gov/pubmed	Search engine for U.S. National Library of Medicine
U.S. Pharmacopeial Convention*	http://www.usp.org/	Dietary supplement monographs and product quality information

Common herbs in KTR

- Echinacea
  - No inhibitory or inductive effects on CYP2D6, CYP2C9, or P-gp in human studies.
  - Conflicting results about effects on CYP1A2 and CYP3A4 (CNI and mTORi)
  - Immune Enhancing Effects; possible interaction with IS
  - Avoid in SOT
- St. John’s wort (available in different brand names; Hypiran, Hypicum…)
  - Potent inducer of CYP3A4 and P-gp. ▼ CNI level and predispose to Rejection
  - Avoid in SOT
- Cat's claw, Milk thistle, Ginseng
  - Immune Enhancing Effects; avoid

❖ Curcumin

- Case report of Acute CNI toxicity
- Unknown mechanism
- It’s best to avoid as routine supplementation and Limit dietary intake

❖ Grapefruit juice (furanocoumarins which include bergamottin)

- Inhibits CYP3A4 in gut ▲ CNI level (15-85%)
- Some may use this Grapefruit juice to save money ! (like diltiazem); to risky and not recommended
- Avoid whole grapefruit and juice in SOT

❖ Green tea and ginger

- Green tea **inhibit** P-gp, OATP1A1, or OATP1A2
- Possible increase in level of CNI; avoid

❖Other sources of Furocoumarins (quercetin, naringin, and bergamottin; inhibit CYP3A4)

- Citrus aurantium and pomegranate
- Increases level of CNI and mTORI
- Limit the using to routine need

❖ Garlic

- Decrease concentrations of drugs that are transported by P-gp
- Interaction with haemostatic agent
- Avoid in supplementation dose

Back to case; pharmacist advice:

- Avoid Echinacea and other immune-stimulating supplement
- Avoid the using of any herbal tea and herbal supplement without consulting their primary health care provider.

Warfarin and digoxin!

- 61 Y/O male admitted to hospital for DVT
- Pharmacotherapy consultant was requested for no increase in INR despite Warfarin 7.5 mg daily from 4 days ago (INR = 1.6).
- **PMH**: Hypothyroidism from 2 weeks ago, HF, HTN
- DH: :Levotheyroxine 50 mcg daily, valsartan 80 mg BD, bisoprolol 5 mg daily, spironolactone 25 mg daily, digoxin 125 mcg daily, amlodipine 5 mg daily,
- **HH**: cigarette smoking (15 cigarette per day) from 4 years ago
- Current TSH: 9.8 mIU/ml

❖ Warfarin in hypothyroidism:

- Untreated or uncontrolled hypothyroid result it ▼ in both the metabolism and synthesis of clotting factors; the response to VKA is delayed or reduced because the clotting factors are eliminated more slowly.
- After successful treatment with T4 and normalization of TSH; increased response may be seen and lower dose of warfarin may be required.
- Monitor INR closely
- Wait at least 3-5 days (5 days may be more accurate) in uncontrolled hypothyroid before any dose adjustment
- When TSH normalized, monitor INR more frequently

❖ Warfarin in hyperthyroidism

- ▲ in both the metabolism and synthesis of clotting factors; no alteration of clotting factors seen in non-anticoagulated;
- Enhanced anticoagulant response may be seen in patient on warfarin (lower dose needed esp. in intital phase of hyperthyroidism)
- Higher dose may be needed after normalization of thyroid function (monitor INR)

❖ Thioamide effects

- especially PTU, has been associated with hypoprothrombinemia, thrombocytopenia, and rarely, bleeding
- Depress BM and clotting factors II, III, VII, IX, X, and XIII (up to 2 mo. After D/C)

- ❖ Digoxin in hyperthyroidism:
  - Lower response rate to Dig due to: intrinsic changes in myocardial function, increase in Vd and Cl
  - Higher dose needed compared to euthyroid patient
  - Adjust dose (reduce) when patient became euthyroid
- ❖ Digoxin in clinical hypothyroidism:
  - Decrease Vd and Cl
  - These patients are inordinately sensitive to the effects of digitalis and require smaller doses to achieve a therapeutic response

Back to case; clinical pharmacist advice:

- Potential reasons for this phenomena:
  - Uncontrolled hypothyroid lead to delayed action of VKA
  - Cigarette smoking induce CYP 2C9 (which involved in metabolism of S enantiomer of warfarin); smoker need higher dose of warfarin

Back to case; clinical pharmacist advice:

- Management:
  - Wait for 5 days and then increase VKA dose (up to 15mg/d) if no increase of INR was seen **OR**
  - Change VKA to alternative OAC (if patient eligible)
  - Monitor INR until patient thyroid function became stable
  - Check Dig level frequently and adjust dose, if needed
  - Smoking cessation


Thank you
The End
Q & A