THE DAY-TO-DAY CLINICAL RELEVANCE of the CYTOCHROME P450 ENZYME SYSTEMS

by dr. tushar shah & dr. n k kumar

A PiE Book
presented on the occasion of
SOS 2019

Symposia On Side-Effects

DEDICATION

The publication and free distribution of this book has been made possible by the support of Mr. Hemendra Sheth and his amazing family.

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AN INTRODUCTION TO CYTOCHROME P450 ENZYME SYSTEMS

The **Cytochrome P450 Enzyme System** is a family of about **fifty enzymes chiefly residing in the liver**. Of the fifty members there are some who are dedicated to just one task. For example, there is a CYP which will just help with the synthesis of oestrogen from testosterone.
And then there are about **twelve CYPs that deal with xenobiotics**.
Xenobiotics are chemical substances which are foreign to the body and must be dealt with after they enter the body. Some xenobiotics are necessary guests like medicinal drugs and some are unwelcome guests like pesticides on your fruits or industrial pollutants. CYPs help inactivating harmful entrants. They also **act upon medicinal agents to either inactivate them after their utility is done or activate them if they are prodrugs**.
Cytochrome P450 is abbreviated as CYP and there are several members in the family and each has a name.
The four most important CYPs with respect to drug metabolism are CYP3A4, CYP2D6, CYP2C9 and CYP2C19.

Why is **cytochrome P450** so called?
'Cyto' stands for cytoplasm where the enzyme resides.
'Chrome' implies that the enzymes are imparted with a colour by **P** - the pigment called haem.
The number 450 has a spectrophotometric connotation not worth discussing here.

If a patient tells you that omeprazole works much better for his acidity but not for his sibling, this may not be his imagination! This actually happens due to genetic polymorphism.

Let me explain the phenomenon of **genetic polymorphism** with respect to the cytochrome P450 enzyme systems.
Each CYP enzyme is encoded by one gene. Each person inherits one genetic allele from each parent. Two alleles thus make up your gene. If you inherit two normal alleles from each parent, you have a normal corresponding CYP enzyme which metabolizes at a predictable rate.

Surprisingly, in the language of genetics a normal allele is called a wild type allele. **Polymorphism occurs when the wild type allele is replaced by a variant allele.**
With respect to CYPs prone to genetic polymorphism, a person can become one of four metabolizer-types depending upon the kind of alleles inherited.
The first variety is what is called **'poor metabolizer'**. This implies low activity of an enzyme.
The second variant is an **'intermediate metabolizer'** with better activity than the poor metabolizer.
The third variant is a **'normal metabolizer'** also known as 'extensive metabolizer'. The fourth variant is an **'ultrarapid metabolizer'** where the enzyme activity is excessive. There are several examples of genetic polymorphism relevant to clinical practice. One in five persons of Asian origin is a poor metabolizer of drugs dependent on **CYP2C19**. Omeprazole is metabolized by this enzyme but not pantoprazole or rabeprazole. The **poor metabolizers therefore have higher levels of omeprazole and have therefore greater benefits in their acid peptic symptoms than persons who are normal metabolizers**.
Another example is that of codeine which is a prodrug activated by **CYP2D6**. Some patients are **poor metabolizers** with respect to CYP2D6. These patients therefore **will not be able to convert the prodrug codeine into the active molecule morphine.** Such patients will have less pain relief with codeine and will also be less likely to become codeine addicts.

If genetic polymorphism is important clinically can we detect polymorphism by genetic testing? We can! In 2004 the US FDA approved the first genotype test designed for clinical use. The test made by Roche is called **Amplichip CYP450. It detects polymorphism of two enzymes - CYP2D6 and CYP2C19**.
Clinically this test, which is available in the US at 500 USD per test (as of the year 2018), is often used by psychiatrists because CYP2D6 metabolizes toxic drugs like risperidone and olanzapine and also many antidepressants.

We doctors have a tough job with respect to applying the knowledge related to CYPs. **We have to memorize a lot of things!** So, what do we need to learn and memorize?

Firstly, **we have to know which drugs are metabolized by the Cytochrome P450 enzyme systems**. For example, amongst beta-blockers, atenolol is not metabolized at all by the CYPs whereas metoprolol is exclusively metabolized by CYPs.

Similarly, **amongst statins, simvastatin and atorvastatin are metabolized by CYPs whereas rosuvastatin is not**.

We also need to **memorize names of drugs which inhibit CYP enzymes**. For example, clarithromycin, erythromycin, itraconazole, quinolones, diltiazem, verapamil, amiodarone are all inhibitors of CYP enzymes.

Within a group, different molecules have different CYP associations. For example, clarithromycin and erythromycin are potent inhibitors of CYP3A4, but azithromycin is only a weak inhibitor making the latter safer as regards drug interactions.

Just as we need to know the inhibitors of CYPs, **we need to know which drugs induce or stimulate the cytochrome P450 enzymes**.

The most important inducer is rifampicin. **Rifampicin stimulates several CYP enzymes.**

We do know therefore that if a patient is on anti-tuberculosis treatment with **rifampicin in it one should not use oral contraceptives** because the induction of CYP enzymes causes a rapid metabolism of OCs.

Within a group again there are differences. For example, **the antiepileptics phenytoin, phenobarbital and carbamazepine are strong inducers of CYPs whereas levetiracetam does not induce any CYP**.

Another important list to memorize is of **drugs that are significantly affected by genetic polymorphism. Important drugs include warfarin, clopidogrel, omeprazole, and multiple antipsychotics and antidepressants**.

About 5% of the population has significant genetic polymorphism related to metabolism of warfarin via CYP. This is the reason why some patients will exhibit either a too strong a response or too weak a response with warfarin.

Let us now quiz ourselves on CYP related drug interactions. Do take it one page at a time as the information overload can be taxing!

CYP QUIZ 1
THEME - MISCELLANEOUS

1. Which **antiarrhythmic drug** is a potent inhibitor of CYP3A4 and may significantly raise blood levels of drugs like warfarin and atorvastatin?

   Answer - **Amiodarone.** Other important CYP3A4 inhibitors include clarithromycin, erythromycin, ciprofloxacin, itraconazole, amongst many others.

2. What is the 'unwanted' side effect of the **CYP3A4 inducer rifampicin** given in a female on oral contraceptives?

   Answer - **Pregnancy.** Rifampicin induces several CYPs and this increases the degradation of drugs like oral contraceptives.

3. Which group of **antiretroviral drugs** are potent inhibitors of CYP3A4?

   Answer - **Protease Inhibitors.** Ritonavir is the strongest 3A4 inhibitor amongst protease inhibitors. Ritonavir when added to lopinavir boosts serum levels of the latter by inhibiting 3A4. Inhibition of 3A4 therefore has been used to an advantage here.

4. Which is the only prostate-specific **alpha blocker** that has drug interactions related to CYP?

   Answer - **Alfuzosin.** Alfuzosin is a substrate of CYPs. Giving a CYP inhibitor like ciprofloxacin to a patient already on alfuzosin may cause levels of alfuzosin to rise causing hypotension and syncope.

5. Name the only **DPP4 inhibitor** which is metabolized by CYPs.

   Answer - **Saxagliptin.** Saxagliptin is metabolized by CYP3A4. Its daily dose should be reduced when CYP3A4 inhibitors like itraconazole are being administered.

CYP QUIZ 2
THEME - CYP INHIBITORS

1. There are **three psychiatric drugs** which are strong inhibitors of CYP2D6. A mnemonic for these three is **Big Freaking Problems** - where B stands for bupropion and F for fluoxetine. What does P stand for?

   Answer - **Paroxetine.** Metoprolol is exclusively metabolized by 2D6. Paroxetine inhibits 2D6. If a patient is taking both, the levels of metoprolol can rise dangerously.

2. Amiodarone is a potent inhibitor of multiple CYP enzymes including 2C9 of which warfarin is a substrate. This may be one reason not to choose warfarin in patients on amiodarone. As an alternative, which **CYP-independent NOAC** (Novel Oral Anticoagulant) can you choose in non-valvar atrial fibrillation?

   Answer - **Dabigatran.** Of the three NOACs available in India as of 2018, dabigatran is the only one not without interactions through CYP enzymes.

3. Amongst **antibiotics**, which group is the most potent inhibitor of 3A4?

   Answer - **Macrolides.** Amongst macrolides, clarithromycin and erythromycin are strong inhibitors of CYP3A4. Azithromycin is a weak inhibitor of 3A4 and hence safer than clarithromycin with respect to drug interactions.

4. Which **fruit juice** will never be served at a seminar of CYPs?

   Answer - **Grapefruit Juice.** A potent CYP3A4 inhibitor, grapefruit juice notoriously increases levels of several substrates of 3A4. For example, it can increase the levels of concomitantly administered atorvastatin predisposing to myopathy.

CYP QUIZ 3
THEME - CYP INDUCERS

1. Name the **antiepileptic** also used classically in trigeminal neuralgia that both **induces 2D6** and is **metabolized** by it.

   Answer - **Carbamazepine.** Since carbamazepine induces the enzyme that also degrades it, its half-life is greatest at the onset of dosing. The half-life gradually decreases as the enzyme gets induced. Hence, carbamazepine should be started at a low dose and gradually increased.

2. Which antiplatelet drug has greater antiplatelet effect in smokers than in non-smokers?

   Answer - **Clopidogrel.** Smoking induces CYP1A2, the enzyme that converts the prodrug clopidogrel to its active metabolite. Smokers therefore have a greater conversion to the active antiplatelet molecule. It is worthwhile to note that nicotine by itself does not induce CYP1A2 and therefore e-cigarettes probably do not interact with clopidogrel.

3. Which drug is considered the most powerful inducer of CYP enzymes?

   Answer - **Rifampicin.** Rifampicin induces multiple CYPs most prominent of which is 3A4. Clinically significant blood level declines can occur of warfarin, oral contraceptives, theophylline, glucocorticoids, amlodipine, digoxin and atorvastatin. Rifampicin has 751 known drug interactions!

4. Cigarette smoking induces CYP1A2. Active smokers therefore require a higher dose of which respiratory drug?

   Answer - **Theophylline.** Theophylline is inactivated by 1A2. Cigarette smoking induces several CYPs including 1A2 and hence smokers require higher doses of theophylline. Clarithromycin, erythromycin, itraconazole, and ciprofloxacin all inhibit 1A2. If theophylline is used in conjunction with these, theophylline toxicity can occur.

CYP QUIZ 4
THEME - GENETIC POLYMORPHISM

1. **CYP2D6** has over 90 variants and **4 phenotypes** (PM, IM, EM, and UM) *. Which drug is converted into morphine by 2D6?

   Answer - **Codeine.** 2D6 is responsible for metabolism of upto 25% of commonly prescribed drugs. In individuals who are genetically deficient in 2D6 (poor metabolizers), codeine will not be converted into morphine making it ineffective as an analgesic. Such patients will also not get addicted to codeine even if they want to!

2. 'Amlichip' is a **CYP450 pharmacogenetic test** by ROCHE to detect genetic polymorphism with respect to 2D6 and 2C19. Chiefly used by psychiatrists in the US, this test predicts the efficacy and ADRs of antipsychotics and anti-depressants. Name two antipsychotics whose pharmacologic action can be predicted by using this test.

   Answer - **Risperidone & Olanzapine.** Many antidepressants and many antipsychotics are metabolized by 2D6. The genetic polymorphism of 2D6 means that different individuals will have different effects of these drugs. For example, poor metabolizers may have therapeutic effect with 10 mg of amitriptyline whereas ultrarapid metabolizers may need 500 mg!

3. Which one of these antidepressants is not a **substrate of CYP** and hence is not susceptible to genetic polymorphism - sertraline, duloxetine, tianeptine?

   Answer - **Tianeptine (Stablon).** It may be useful for us to remember drugs that are not affected by CYP polymorphism. It is estimated that thousands of deaths occur in the US annually due to genetic polymorphism-related drug overdose.

4. **2C19** has only **3 phenotypes** PM, EM, and UM. In which PPI does genetic polymorphism of 2C19 play the largest role?

   Answer - **Omeprazole (and esomeprazole).** A small but significant percentage of the population is a poor metabolizer with respect to 2C19. Each such individual will have higher than usual levels of omeprazole and hence greater relief in dyspepsia and also a greater eradication rate of H. pylori. The only PPI completely independent of CYPs is rabeprazole.

*PM = Poor metabolizers
IM = Intermediate metabolizers
EM = Extensive metabolizers (which is the normal variant)
UM = Ultrarapid metabolizers

CYP QUIZ 5
THEME - PRODRUGS

1. Which one of these **opioid analgesics** is not a prodrug nor a substrate of 2D6 and hence not affected by genetic polymorphism - oxycodone, tramadol, tapentadol?

   Answer - **Tapentadol.** Tapentadaol is not significantly dependent on CYPs. Therefore, unlike codeine and tramadol, it is not susceptible to genetic polymorphism of 2D6 and has more predictable effects.

2. Which **antihypertensive agent** is a prodrug and is metabolized to its active form by 2C9 and is hence susceptible to genetic polymorphism?

   Answer - **Losartan.** Since losartan may be ineffective in a small percentage of patients due to genetic polymorphism of 2C9, one must try another 'sartan' when losartan fails to control BP.

3. Which drug used in **breast cancer** is a prodrug activated by 2D6 and hence susceptible to genetic polymorphism?

   Answer - **Tamoxifen.** In poor metabolizers related to 2D6, tamoxifen is not converted into its active metabolite making such persons more prone to breast cancer recurrences.

4. Which prodrug used as an **antiplatelet** comes with a US FDA boxed warning regarding **CYP2C19 polymorphism** and hence reduced efficacy in some individuals?

   Answer - **Clopidogrel.** In patients with genetically deficient 2C19, clopidogrel may be ineffective as an antiplatelet drug. On the other hand, **prasugrel**, which is converted to its active metabolite by several CYPs, is not susceptible to genetic polymorphism.

CYP QUIZ 6
THEME - MISCELLANEOUS

1. Itraconazole, terbinafine, and fluconazole are CYP inhibitors. Name an **antifungal which is an inducer** of CYP3A4.

   Answer - **Griseofulvin**

2. In a person already on atorvastatin, which antihypertensive drug if added may cause **statin induced myopathy**?

   Answer - **Diltiazem or Verapamil**

3. Which alternative medicine for depression related to **hypericum perforatum** is used widely in the US and is a strong 3A4 inducer?

   Answer - **St. John's vort**

4. If itraconazole is given to a patient on **ranolazine**, levels of ranolazine can rise enough to cause death. How?

   Answer - **QT_c prolongation & ventricular tachyarrhythmia**

5. Diazepam and alprazolam are substrates of 3A4. Strong 3A4 inhibitors can increase blood levels of diazepam and alprazolam. Which **benzodiazepine** is independent of CYP3A4?

   Answer - **Lorazepam**

6. All **nitroimidazoles** (like metronidazole) are inhibitors of 2C9. If a person on warfarin is to be treated for amoebiasis, you should try to avoid nitroimidazoles. Which drug will you then use?

   Answer - **Nitazoxanide**

CYP QUIZ 7
THEME - NEUROPSYCHIATRIC DRUGS

1. Two strong inducers of CYP3A4 from the domain of neuropsychiatry are **'CARB & BARB'**. If BARB stands for Barbiturate, what does CARB stand for?

   Answer - **Carbamazepine**.

2. Can you predict what happens when a patient on **carbamazepine** is given sertraline as an antidepressant?

   Answer - **Sertraline** is metabolized by CYP3A4 which is induced by carbamazepine. Hence such patients may not show clinical efficacy with sertraline.

3. Can you predict what might happen when a patient on **fluoxetine or paroxetine** is given amitriptyline?

   Answer - The adverse drug reactions of **amitriptyline** might increase as fluoxetine and paroxetine inhibit CYP2D6 which metabolizes amitriptyline.

4. Can you predict what might happen when a patient on **fluoxetine or paroxetine** is given codeine for pain management?

   Answer - In this situation, **codeine** may not be converted adequately to its active metabolite morphine as fluoxetine and paroxetine inhibit CYP2D6.

ITRACONAZOLE, CLARITHROMYCIN AND DRUG-DRUG INTERACTIONS

Both itraconazole and clarithromycin are **strong inhibitors of CYP3A4** and are fairly commonly prescribed.

Thus, **a person prescribed itraconazole or clarithromycin may**

1. Exhibit hypotension and greater leg oedema if on **amlodipine**.
2. May bleed if on **warfarin, apixaban** or **rivaroxaban**.
3. May have myopathy if on **atorvastatin** or **simvastatin**.
4. May have excessive sedation if on **alprazolam** or **diazepam**.
5. May have postural hypotension if on **alfuzosin**.
6. May have hyperkalemia if on **eplerenone**.
7. May have QT_c prolongation if on **ranolazine**.
8. May have bradycardia if on **ivabradine**.

TEN DICTUMS

BASED ON CYP-RELATED DRUG-DRUG INTERACTIONS

1. **Prefer azithromycin** over clarithromycin whenever possible.

2. **Prefer rosuvastatin** over atorvastatin at all times.

3. **Double check** all existing medicines before starting **amiodarone**.

4. **Prefer tapentadol** over tramadol.

5. **Try omeprazole when other PPIs have not been very effective.** Avoid omeprazole in patients who are on clopidogrel.

6. **Discard alfuzosin** and use only tamsulosin or silodosin.

7. **Avoid phenytoin and phenobarbitone** as much as possible.

8. **Prefer oxcarbazepine over carbamazepine** whenever possible.

9. **Double check** existing medications before prescribing **itraconazole**.

10. **Diligently check online** for drug interactions before prescribing any new drug to patients on **warfarin** or acitrom.

CYP3A4 INHIBITORS

The following will reduce the action of CYP3A4 and hence increase the blood levels of drugs metabolized by it.

Antibiotics - Clarithromycin and erythromycin (but not azithromycin).

Calcium-channel blockers - Verapamil and diltiazem but not amlodipine.

Antifungals - Itraconazole and ketoconazole are strong inhibitors while Fluconazole is a weak inhibitor.

Protease inhibitors used for HIV/AIDS - e.g. Ritonavir.

Amiodarone.

Grapefruit and grapefruit juice.

Do remember that CYP3A4 is the most important CYP. It metabolizes more than 50% of drugs metabolized by CYPs.

CYP INDUCERS

These drugs stimulate CYP enzymes and hence reduce blood levels of drugs degraded by them or increase the conversion of prodrugs to active drugs.

Rifampicin - it is a potent inducer of at least 4 important CYPs including CYP3A4.

Antiepileptics - Carbamazepine, phenytoin and phenobarbital - they too induce several CYPs.

Glucocorticoids.

Griseofulvin - While most antifungals are inhibitors of CYPs, griseofulvin is an exception.

Hypericum perforatum is a popular homeopathic medicine marketed for depression in the US under the name St. John's vort. It is a CYP inducer. Interestingly, it is an OTC drug.

N.B. CYP inducers rifampicin and the older antiepileptic drugs can reduce the efficacy of oral contraceptives, benzodiazepines, simvastatin, atorvastatin, amlodipine and sildenafil.

Tobacco smoking (by inducing CYP1A2) can reduce the efficacy of theophylline necessitating an increase in dose in COPD patients who continue to smoke.

PSYCHIATRIC DRUGS AND CYPs

Statistically, the largest prescribers of anxiolytic and antidepressant drugs are NOT psychiatrists but primary care physicians.

Fluoxetine, paroxetine & bupropion are antidepressants which inhibit CYP2D6 and can hence raise blood levels of metoprolol, of tricyclic antidepressants like amitriptyline, and of haloperidol.

Another antidepressant **fluvoxamine inhibits CYP3A4**. It can thus increase blood levels of benzodiazepines like diazepam & alprazolam.

It is important to note that the antidepressants **citalopram, sertraline, venlafaxine & duloxetine are less likely to have CYP related interactions** at their usual doses.

The antidepressant **mirtazepine has no CYP related interaction**.

Many antidepressants & antipsychotics are inactivated by CYP2D6, an enzyme that exhibits significant genetic polymorphism. This is why we clinically observe significant differences in patient-to-patient response to these drugs.

ANTIFUNGAL DRUGS AND CYPs

Itraconazole and ketoconazole are strong inhibitors of the CYP3A4 enzyme.
Fluconazole is an inhibitor but only at doses above 200mg/d.
Do note that oral ketoconazole use is strongly discouraged because of severe hepatotoxicity.

To repeat what has already been posted before, **a person prescribed itraconazole may**

1. Exhibit hypotension and greater leg oedema if on **amlodipine**.
2. May bleed if on **warfarin, apixaban** or **rivaroxaban**.
3. May have myopathy if on **atorvastatin** or **simvastatin**.
4. May have excessive sedation if on **alprazolam** or **diazepam**.
5. May have postural hypotension if on **alfuzosin**.
6. May have hyperkalemia if on **eplerenone**.
7. May have QT_c prolongation if on **ranolazine**.
8. May have bradycardia if on **ivabradine**.

WARFARIN AND CYPs

Warfarin is metabolised by three different CYPs. Inhibitors of these enzymes can increase blood levels of warfarin.

CYP2C9 inhibitors like amiodarone, fluconazole, metronidazole, and fluoxetine increase warfarin levels and bleeding potential. Thus, for example, if you have to give metronidazole (or a related imidazole) in a person on warfarin, reduce the dose of warfarin for those days, alert the patient and monitor INR closely. Alternately, you can replace metronidazole.

CYP3A4 also metabolises warfarin. Therefore, **inhibitors of CYP3A4** can increase warfarin blood levels. For example, it is important to avoid the combination of warfarin with diltiazem or verapamil.

CYP1A2 metabolises warfarin. Ciprofloxacin and levofloxacin are inhibitors of this enzyme and thus should be avoided in patients on warfarin.

It is relevant here to note that amongst the newer anticoagulants, dabigatran (Pradaxa) is not a substrate of CYPs while rivaroxaban (Xarelto) and apixaban (Eliquis) are significantly metabolised by CYPs.

CARDIAC DRUGS AND CYPs

In a patient on multiple cardiac drugs, CYP related drug interactions are aplenty. It is important to remember that the **calcium channel blockers verapamil & diltiazem inhibit CYP3A4** and thus may increase the serum levels and toxicity of simvastatin and atorvastatin. Calcium channel blockers like amlodipine and cilnidipine do not inhibit CYP3A4.

Amiodarone is a potent inhibitor of multiple CYP enzymes including CYP3A4. Thus, **if you need to give a statin with amiodarone, choose rosuvastatin**.

Amiodarone also inhibits CYP2C9, of which warfarin is a substrate. Thus, **amiodarone can dangerously increase blood levels of warfarin**.

The antidepressants **paroxetine & fluoxetine inhibit CYP2D6** which is the sole metabolizer of **metoprolol & nebivolol**.
If a patient on metoprolol is given paroxetine the levels of metoprolol increase. This may cause hypotension.

It is useful to note here that bisoprolol has 50% renal excretion while atenolol has 100% renal excretion.

DRUG-DRUG INTERACTIONS
UNRELATED TO CYP ENZYMES

1. **Metformin** should be withheld 48 hours prior to and 48 hours after use of **contrast media** to reduce the risk of contrast-induced nephropathy.

2. A combination of **pioglitazone and NSAIDs** increases the risk of heart failure and fluid retention.

3. Patients on antidiabetic agents may experience **hypoglycaemia unawareness** if **beta-blockers** are also being given.

4. **Digoxin and diuretics** are often co-administered. Hypokalaemia caused by diuretics will increase digoxin toxicity. Serum potassium must be monitored.

5. Co-administration of **low dose aspirin and a thiazide diuretic** can cause significant hyperuricemia.

6. Co-administration of **steroids and diuretics** can cause significant hypokalaemia with each drug contributing.

7. Potassium sparing diuretics like **spironolactone** should be used with caution in patients receiving **ACE inhibitors** or **angiotensin receptor blockers**. The combination can cause hyperkalaemia.

8. Giving **sildenafil or tadalafil** in patients on **nitrates** can cause severe hypotension and may precipitate an acute coronary syndrome.

9. **Quinolones** should be given 4 hours away from **calcium, iron, and liquid antacids** as these preparations reduce the absorption of quinolones.

10. **Linezolid** should be avoided in patients receiving **SSRIs** as this combination may precipitate the **serotonin syndrome**.

11. **Paracetamol** can increase the blood levels of **warfarin** causing bleeding diatheses.

12. A combination of **fenofibrate and a statin** increases the chances of myopathy.

13. Giving **tramadol** in patients on **SSRIs** can cause the **serotonin syndrome**.

14. All **NSAIDs reduce the effect of all antihypertensive drugs except of calcium channel blockers**.

15. **Cotrimoxazole can cause hyperkalaemia** especially in the elderly and in patients of CKD. Hence use of cotrimoxazole should be avoided in patients on **ACE Inhibitors and ARBs**.

16. A combination of **doxycycline and isotretinoin** or of **vitamin A and isotretinoin** can precipitate benign intracranial hypertension.

17. Administering xanthine-oxidase inhibitors like **allopurinol or febuxostat** can raise blood levels of **pyrazinamide** as the latter is metabolized by xanthine-oxidase.

18. Administration of **fluoroquinolones** in diabetic patients receiving **oral anti-diabetic drugs** may cause either hypoglycaemia or hyperglycaemia.

19. There are many examples of additive adverse effects of drugs used together. For example, if diuretics are administered in patients on **SGLT2 inhibitors** volume depletion can occur due to diuresis caused by both. Another such example is the occurrence of GI bleed in patients receiving both **steroids and NSAIDs.**

20. If a patient of bipolar disorder is on **lithium**, one should **reduce its dose by half if a diuretic or an NSAID is being co-prescribed** as these can reduce the renal elimination of lithium.

The list is unending, but we have to end the book somewhere! This seems to be the right place!