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### CYP 450: Coming to a Drug Near You

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Experts in pediatrics, Advocates for children. 1

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### Speaker Disclosure

- No conflicts of interest




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### Objectives

- Examine the CYP450 enzyme system and its role in metabolism of common pediatric medications and foods (including role of polymorphisms)
- Discuss the pharmacokinetics/genomics related to CYP450 inducers and inhibitors
- Identify common drug and food interactions impacted by the CYP450 enzyme pathway
- Formulate recommendations for practice to reduce or eliminate drug-drug interactions caused by the CYP450 enzyme pathways
- Identify a potential drug-drug interaction due to the CYP450 enzyme pathway




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### Why Discuss the CYP450 Enzyme Pathway?

- Drug-drug interactions can be difficult to anticipate
- The CYP 450 enzyme pathway impacts drug metabolism on many commonly prescribed pediatric medications
- 90% of drugs metabolized by CYP450 pathway



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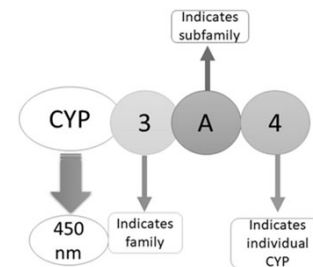
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## Cytochrome P450 Enzyme Pathway

- Detoxification
- Biosynthesis of cholesterol, steroids, prostacyclins, thromboxane A2, other lipids
- Drug metabolism
- Polymorphisms
- Ethnic variability
- CYP3A4 and CYP2D6

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Stipp, M.C. & Acco, A. (2021) Involvement of cytochrome P450 enzymes in inflammation and cancer: a review. *Cancer Chemotherapies and Pharmacology*, 87, 295–309.  
<https://doi.org/10.1007/s00280-020-04181-2>

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## Definitions

- **Inhibitors** *increase* drug concentration by *decreasing* enzyme (metabolic) activity
- **Inducers** *reduce* drug concentration by *increasing* enzyme (metabolic) activity
- **Polymorphisms**-variability in gene expression of CYP450 enzymes that impact drug variability and response
- **Pharmacogenetics**-variations in DNA sequence of specific genes affect drug response, change plasma drug concentration
- **Pharmacodynamics**-drugs interacting at receptors

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## Metabolizer Categories

- **Poor:** increased side effects or ineffective
- **Intermediate:** may not process as well as normal
- **Normal:** standard dosing effective
- **Ultrarapid:** may need higher than normal dose or change medication

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### CYP450

- **Liver-expression most abundant**
- Breast
- Gut
- Colon and small intestine

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### CYP450

- Inhibitor-certain drugs inhibit p450, increasing drug levels
- Inducers-certain drugs induce p450, decreasing drug levels
- Polymorphisms impact drug effects

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### Normal Drug Metabolism

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### Inhibitors SICKFACES.COM Group

<b>S</b> Sodium valproate	<b>C</b> Cranberry juice
<b>I</b> Isoniazid	<b>O</b> Omeprazole
<b>C</b> Cimetidine	<b>M</b> Metronidazole
<b>K</b> Ketoconazole	<b>GP</b> Grapefruit juice
<b>F</b> Fluconazole	
<b>A</b> Alcohol (binge), amiodarone, acetaminophen	
<b>C</b> Ciprofloxacin	
<b>E</b> Erythromycin (macrolides)	
<b>S</b> Sulfonamides, SSRIs	

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### Inhibitor-Decreases Drug Metabolism



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### Inducers BS CRAP GPS

- B** Barbiturates
- S** St. Johns Wort
- C** Carbamazepine
- R** Rifampicin
- A** Alcohol (chronic)
- P** Phenytoin
- G** Griseofulvin
- P** Phenobarbital
- S** Sulfonylureas



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### Inducer-Increases Drug Metabolism



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### Assessing for Polymorphism

- **Family history!**
- Genetic testing-Amplichip
  - cheek swab
  - saliva
  - blood

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## Why Should We Care?

- **DDIs more than 49% in hospitalized children**
  - Infants: day 1 with 22% exposed potential, 32% day 30
  - PICU 75% exposed, 69% had major potential DDI
- Area Under the Curve (AUC): Measure of total systemic exposure to the drug
- MIC minimum inhibitory concentration (MIC): lowest concentration for effectiveness

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## Pediatric Medications impacted by CYP450

- |                               |   |
|-------------------------------|---|
| • Ondansetron                 | • Tacrolimus, cyclosporine                    |
| • Vincristine                 | • Escitalopram                                |
| • Viloxazine (Quelbee)        | • Spironolactone - inhibitor                  |
| • Dextromethorphan            | • Caffeine                                    |
| • Estrogen-progestin products | • Imipramine, amitriptyline (TCA's) - inducer |
| • Lansoprazole                | • Methadone                                   |
| • Risperidone - inhibitor     | • <b>Oxycodone, codeine</b>                   |

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## Herbal Interactions

- Echinacea (purple coneflower) - inhibitor
- Ginkgo Biloba - inhibitor
- St. John's wort - inducer
- Goldenseal - inhibitor
- Green tea - inducer and inhibitor

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[illegible]

## Case Study - Celia

Celia

Celia is a 17 year-old adolescent, hx migraines, but overall healthy. She presents with complaint of new onset blurred vision, feeling "anxious" and sweaty, and loss of appetite for the past 6 weeks. No increase in migraine number or change in symptoms.

## Medications:

- Oral contraceptive
- Imipramine prn, 12 times this past month
- Fluoxetine 20mg daily
- Significant FHx: mother with post partum depression, hx migraines on imipramine prn
  - negative neurological issues, grandmother had breast cancer, grandfather died age 60 of MI.

Celia

- PE:

- HR 100, BP 120/78
- Weight: 120lbs, decrease 2 pounds since visit 3 months ago
- Skin warm, dry
- Abdomen: palpable stool LLQ
- Otherwise normal including neuro exam

### What do we know?

- Oral contraceptives - easily impacted by inducers
- Imipramine – inducer
- Fluoxetine – inhibitor
- What do we need to know?
  - Family history!
  - Time on these medications
    - OC x 3 years
    - Imipramine 2 years on current dose
    - Fluoxetine x 8 weeks

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### What do we think?

- Differentials?

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### Diagnosis

- Elevated levels of imipramine due to fluoxetine
- SSRIs are CYP450 inhibitors

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### CYP450 and COVID-19

- CYP450 enzymes downregulated during inflammation and infection
- Isoniazid, ritonavir, remdesivir, ivermectin, azithromycin, montelukast, acetylsalicylic acid
- Azithromycin/warfarin
- Inhibitors or inducers?
- Possible side effects
  - Hepatotoxicity
  - Thromboembolism or bleeding
  - Treatment failure

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## Objectives - Recap

- Examine the CYP450 enzyme system and its role in metabolism of common pediatric medications and foods
- Describe the pharmacokinetics/genomics related to CYP450 inducers and inhibitors
- Identify common drug and food interactions impacted by the CYP450 enzyme pathway
- Formulate recommendations for practice to reduce or eliminate drug-drug interactions caused by the CYP450 enzyme pathways
- Using a case study, identify a potential drug-drug interaction due to the CYP450 enzyme pathway

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## Key Takeaways

- Check for P450 interactions-apps are available
- Inducer, may require decreased dose; Inhibitor-increased dose
- Caution with herbal preparations
- Know before you prescribe
- **Family history!**

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# Thank you!

## Questions?

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