- Pharmacology of Pain
- Pain Urgencies and Emergencies or how patients can make things interesting
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Disclosures....

None



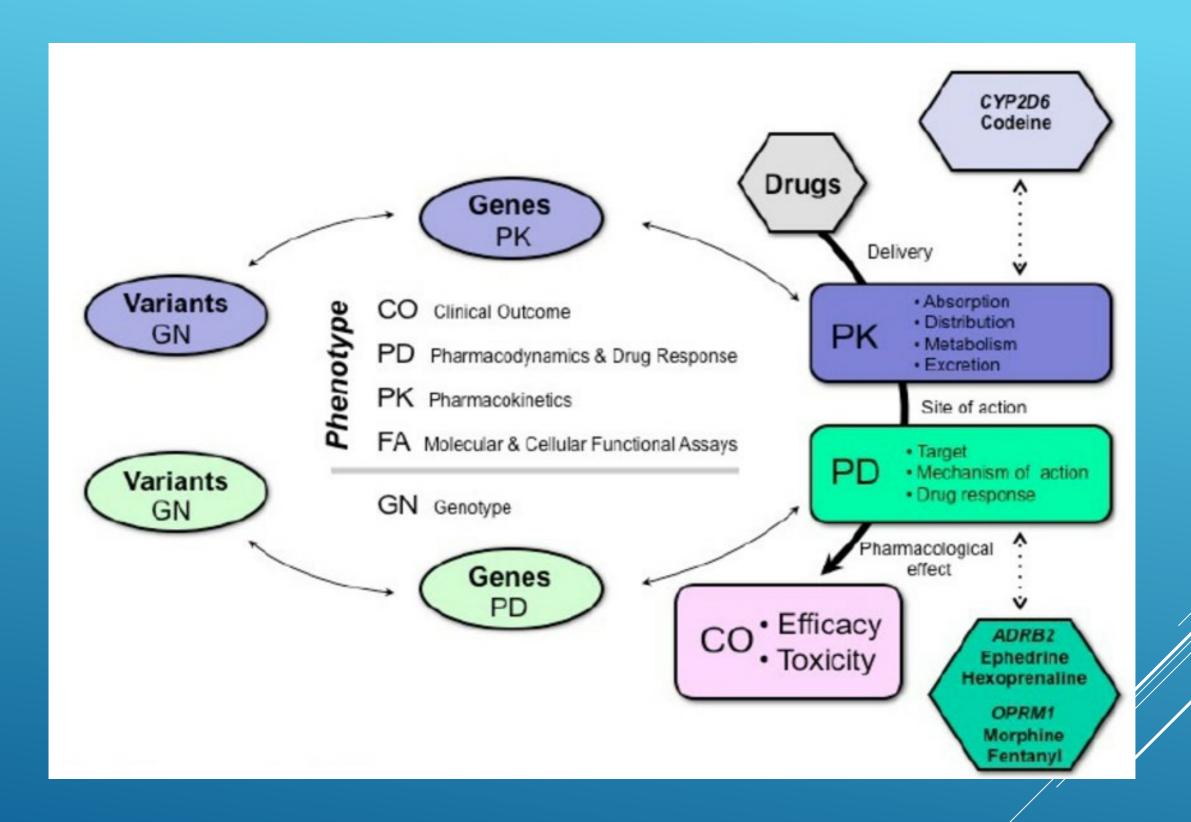
Goals of Discussion

- Develop a rational approach to management of Non neuropathic and neuropathic pain syndromes
- Utilize basic concepts in pharmacology / neurophysiology
- Concepts of metabolism, Pheno-conversion, genetics and genomics

- ▶ Terminology
- Genetics the study of individual genes, heredity, and genetic variations
- Genomics The study of an organism's entire genome. Looks at how genes interact with one another, and the environments' role on affecting them
- ▶ Pheno-conversion- the phenomenon where an individual's drug metabolism (their actual ability to metabolize drugs) differs from what is predicted based upon their genotype(UM,IM,PM) This is due to non genetic factors smoking, other medications, lifestyle choices

- Pharmacogenomics- The study of how a person's genes affect their response to a drug. Allows the prescriber to move away from "one size fits all" approach to a more personalized approach.
- Pharmacodynamics- Focuses on what a drug does to the body. It investigates biochemical ,physiological and molecular effects of drugs on living systems. Looks at drug –receptor interaction ,Dose –response relationships, Mechanism of action , and factors influencing responses – aging , diseases, and other drugs

TERMINOLOGY CONTINUED



- ▶ Let's talk about pain and Opiates
- ➤ Opiates are good!
- ▶ Opiates are Bad!
- ▶ Opiates are Ugly!
- ➤ This is confusing. I have a headache and need Hydromorphone – just kidding, but maybe not. It's potentially a rational choice as we shall see.

- ▶ Why pick on Opiates?
- Many reasons
- Highly regulated
- Lots of side effects
- Hypersensitization over time
- Misuse potential
- What you don't know you don't know will get you and your patient into trouble
- Problem is sometimes Opiates are your best option



Metabolism of Opiates and all the ways to mess it up.

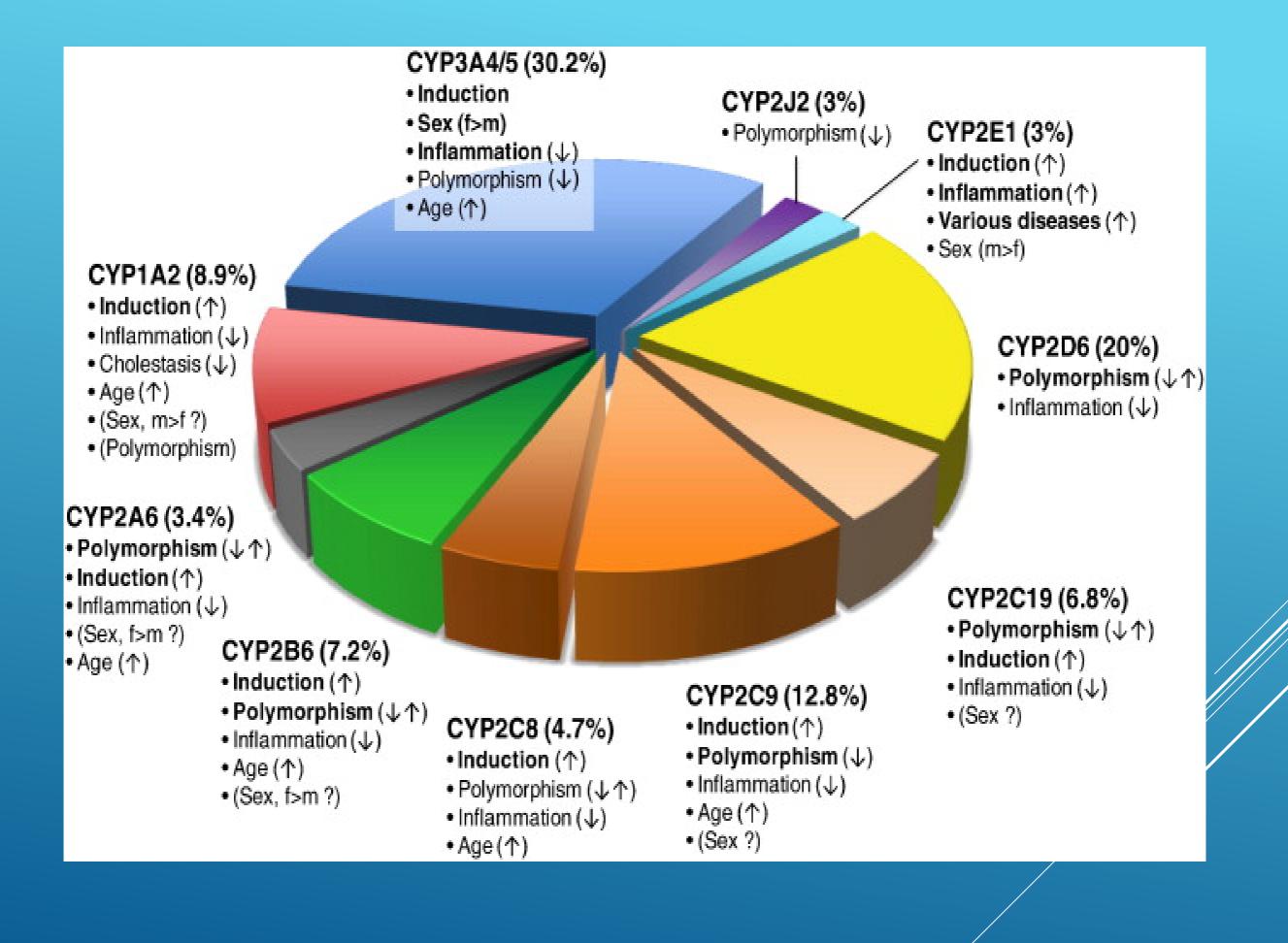


Table 1

Inhibitory Effect of SSRIs on CYP-450 Isoenzymes

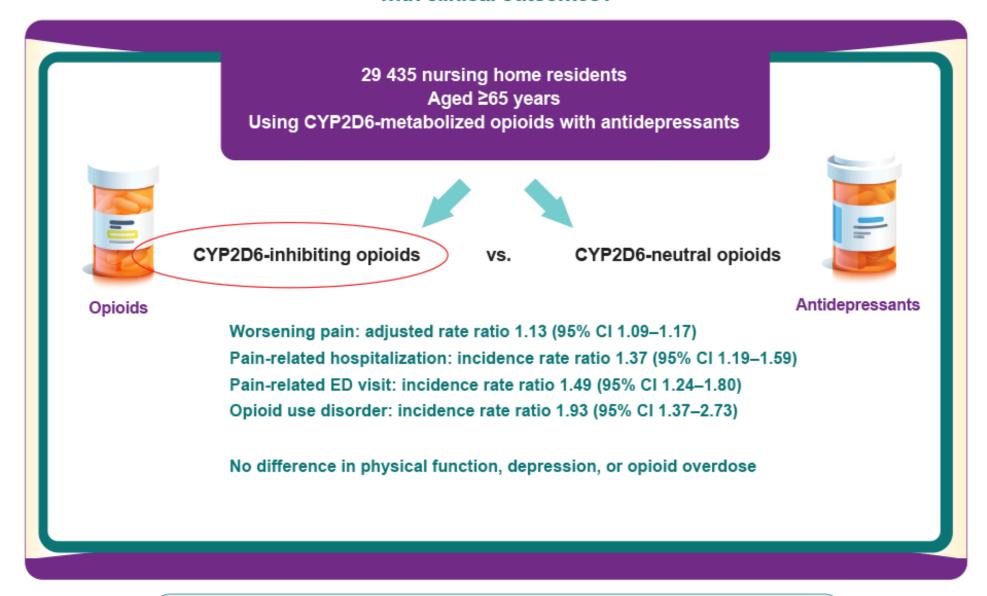
CYP-450 Isoenzymes					
Agent	CYP-1A2	CYP-2C9	CYP-2C19	CYP-2D6	CYP-3A4
Citalopram	0	0	0	+	0
Fluoxetine	+	++	+/++	+++	+/++
Fluvoxamine	+++	++	+++	+	++
Mirtazapine	0	0	0	+	0
Nefazodone	0	0	0	+	+++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+	+/++	+
Venlafaxine	0	0	0	+	+

SSRI: selective serotonin reuptake inhibitor; CYP: cytochrome P; 0: minimal/no inhibition; +: mild inhibition; ++: moderate inhibition; ++: potent inhibition.

Source: References 12, 13, 14.

- What does this mean
- Concept of phenoconversion As noted earlier but worth repeating: The phenomenon where and individuals drug metabolism phenotype (there actual ability to metabolize a drug)differs from their genotype(UM,IM,PM) due to non genetic factors (medications, lifestyle choices health)

Is use of CYP2D6-metabolized opioids with antidepressants associated with clinical outcomes?





Wei Y-JJ, Winterstein AG, Schmidt S, et al. Clinical and adverse outcomes associated with concomitant use of CYP2D6-metabolized opioids with antidepressants in older nursing home residents. A target trial emulation study. Ann Intern Med. 23 July 2024. [Epub ahead of print]. doi:10.7326/M23-3109 http://acpjournals.org/doi/10.7326/M23-3109

- Original Research
- ▶ 23 July 2024
- Clinical and Adverse Outcomes Associated With Concomitant Use of CYP2D6-Metabolized Opioids With Antidepressants in Older Nursing Home Residents: A Target Trial Emulation Study
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- > Results:
- ➤ Among 29 435 identified residents, use of CYP2D6-metabolized opioids concomitantly with CYP2D6-inhibiting (vs. CYP2D6-neutral) antidepressants was associated with a higher adjusted rate ratio of worsening pain (1.13 [95% CI, 1.09 to 1.17]) and higher adjusted incidence rate ratios of pain-related hospitalization (1.37 [CI, 1.19 to 1.59]), pain-related ED visit (1.49 [CI, 1.24 to 1.80]), and OUD (1.93 [CI, 1.37 to 2.73]), with no difference in physical function, depression, and opioid overdose.

AMONG OPIOID-TREATED ONCOLOGY PATIENTS

- ► Let's look at the CYP 2D6 pathway
- ▶ Why- metabolism of Opiates and antidepressants
- ▶ No pain patient is ever on both

- Real life examples
- Case 1 78-year-old female status post ORIF with CMN for intertrochanteric hip fracture with subtrochanteric extension
- Construct is stable post op and patient is WBAT
- ➤ Pain is 10/10 post operative and non-responsive to hydrocodone at 5 to 10 mg Q 4 dosing prn pain.
- She is changed to Oxycodone 5-10 mg Q 4 prn pain with slight improvement in pain score to 8-9/10
- She is admitted to rehab for acute rehab services, and pain control.

- ➤ What's going on ?
- ▶ First is she sedated No
- Second is pain control adequate No / will not participate in therapy
- Third- Is she a drug seeker / or does she have a history of prior opioid use with high tolerance – No
- Lets look at her history
- ► HTN, Diet controlled DM type 2 ,HLD, Anxiety
- Meds Lisinopril, Atorvastatin, prn meloxicam for arthritis pain, Multi vitamin, Prozac

- ▶ Now it all makes sense. We now know the problem
- What is the problem ?
- How do we fix the problem? What are our options
- Simple fix, and with the fix, pain overnight goes to 0-1/10, and we have a fully participating patient who goes home in 10 days

- Case 2 Acute care hospitals and patient families can make for entertaining times.
- 72-year-old female with longstanding chronic pain. History of multiple lumbar spine surgeries with instrumentation for chronic back pain. Patient is on chronic opiates for her chronic pain.
- Admitted to rehab after a 3 day stay in an acute care hospital for encephalopathy – work upon presentation to the acute care hospital revealed UTI with impending sepsis – antibiotics initiated, and patient cleared cognitively

- On presentation to rehab- patient was noted to complain of back pain 10/10 – her chronic Oxycodone at home was 10 mg 4x/day with prn Tramadol /Tylenol Q 6. Pain control per the patient and family was suboptimal. An interesting combination, but people are on interesting combinations. Keeps Doctors young and curious
- Pain poorly controlled on above cocktail.
 Oxycodone increased from 10 mg Q4 to 15 mg Q4 as patients' family demanded increase as mom is very tolerant of pain medications (a potential canary in the coal mine)
- After 3 days on high dose opiates at the rehab hospital the patient suddenly became obtunded with hyperventilation – required Narcan x 2

- What happened
- ► Let's look at PMH
- ► HTN on amlodipine
- ► HLD on simvastatin
- ► Type 2 diabetes on Metformin
- Chronic pain on 10 mg Q 4 Oxycodone for years at home, and per the patient and family suboptimal pain control – consideration as outpatient given for possible OxyContin and prn oxycodone – a bit of head scratcher, but ???

- ► Meds
- Amlodipine, Metformin, Simvastatin
- Wellbutrin at home- It was stopped at the acute care hospital and was never restarted and no mention made on the DC summary (active metabolite half life is greater than 2 days)
- Wellbutrin is a very potent inhibitor of CYP2D when it finally cleared her system, she garnered the full effects of the opiate. Had this been Prozac, the same thing would have occurred only much later at home. Drugs will get you into trouble and sometimes stopping them can be a problem.

 You must know your pain medications, how they work and how other meds – particularly antidepressants can affect pain medications

Patient satisfaction for pain control after a teaching module at our acute rehab hospital improved from 75 % to sustained for past 4 years, to > 95 % after teaching about phenoconversion.

Neuropathic Pain

- Or it burns, stings, buzzes tingles and sometimes feels like someone is ripping my arm/leg off.
- Neurotransmitters and ion channels implicated in pain modulation
- Acetylcholine /Serotonin / Norepinephrine
- CGRP / GABA
- Na + and Ca 2+ ion channels
- Just to name a few. Good news and bad news: Lots of options- good /bad?

- Options are good.
- Most common mistakes in medication management
- Monotherapy
- If one doesn't work / Change to another and stop the first - Monotherapy

- Sodium ion channel modulators –Zonisamide, Topamax
- GABA pathway –Baclofen, Topamax
- Glutamate receptor antagonism Topamax
- Calcium Channel modulation Zonisamide, Gabapentin
- Calcitonin receptor modulation Miacalcin nasal spray
- ► SSNRI Serotonin / NE Duloxetine, Venlafaxine
- SSRI's caution with Fluoxetine, Paroxetine
- NE/Dopamine reuptake inhibitors Bupropion- caution

- Multifaceted medication management
- Take advantage of multiple sites to impact on pain. Various ion channels and various receptors
- Optimize pain control while balancing side effect profiles
- Base of the pyramid Gabapentin get dose to 1800-2400 mg /day range in divided doses then start adding options – understand the transport system of the drug – active protein transport mechanism
- Look at when is pain at its worst. What does it feel like. What helps, what doesn't.

- Things Hearned over too many years
- Neuritic itch responds well to Zonisamide excellent response clinically in my burn patients
- Deep squeezing / aching / throbbing pain responds well to Duloxetine
- Bone pain associated with fractures complicating neuropathic pain - Calcitonin
- Understand impact of SSRI's on CYP 2D6

- Goals Hopefully achieved
- Introduce and increase comfort in exploring medication options and combinations
- Help develop a rational approach to pharmacology
- Emphasize rationale for multi medication approach to control of neuropathic pain