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Best practices around Safer Prescribing of Opioids

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Objectives

At the end of this presentation, participants should be able to:

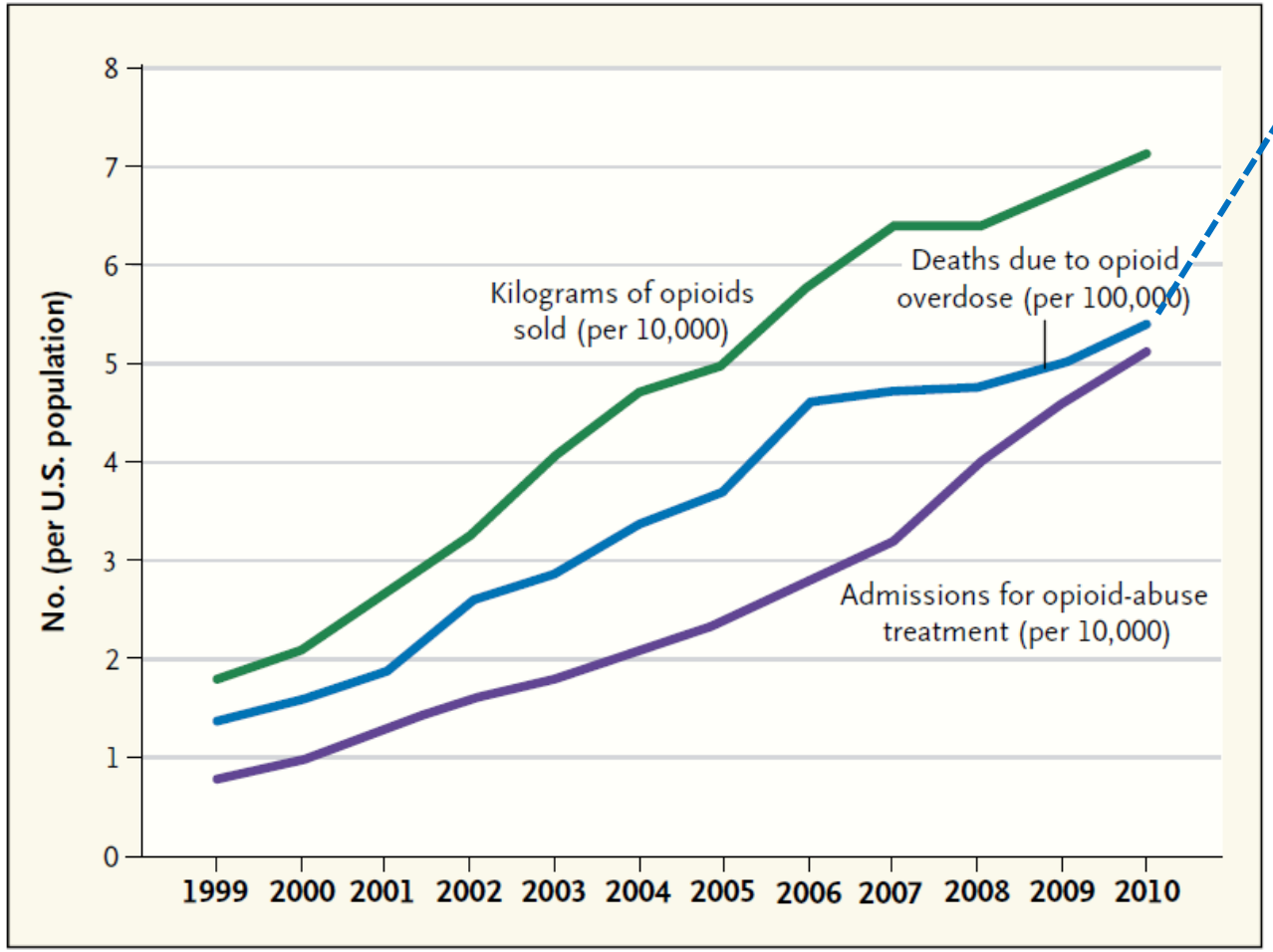
- Discuss how drug interactions and genetic variants influence opioid response,
- Describe strategies for mitigating drug interactions influencing opioid response, and
- Apply mitigating strategies to patient cases to practice safer prescribing of opioids.

Opioid-Related Drug Interactions
Epidemic

"The crisis of opioid addiction is a public health tragedy of enormous proportions. We need to confront it like any explosive epidemic."

Remarks by Scott Gottlieb, MD, U.S. FDA Commissioner on July 10, 2017 during the FDA's Scientific Meeting on Opioids

Opioid Epidemic



Opioid Sales, Admissions for Opioid-Abuse Treatment, and Deaths Due to Opioid Overdose in the United States, 1999–2010.

The rate of death from ODs of **prescription opioids** in the United States more than quadrupled between 1999 and 2010, far exceeding the combined death toll from cocaine & heroin ODs

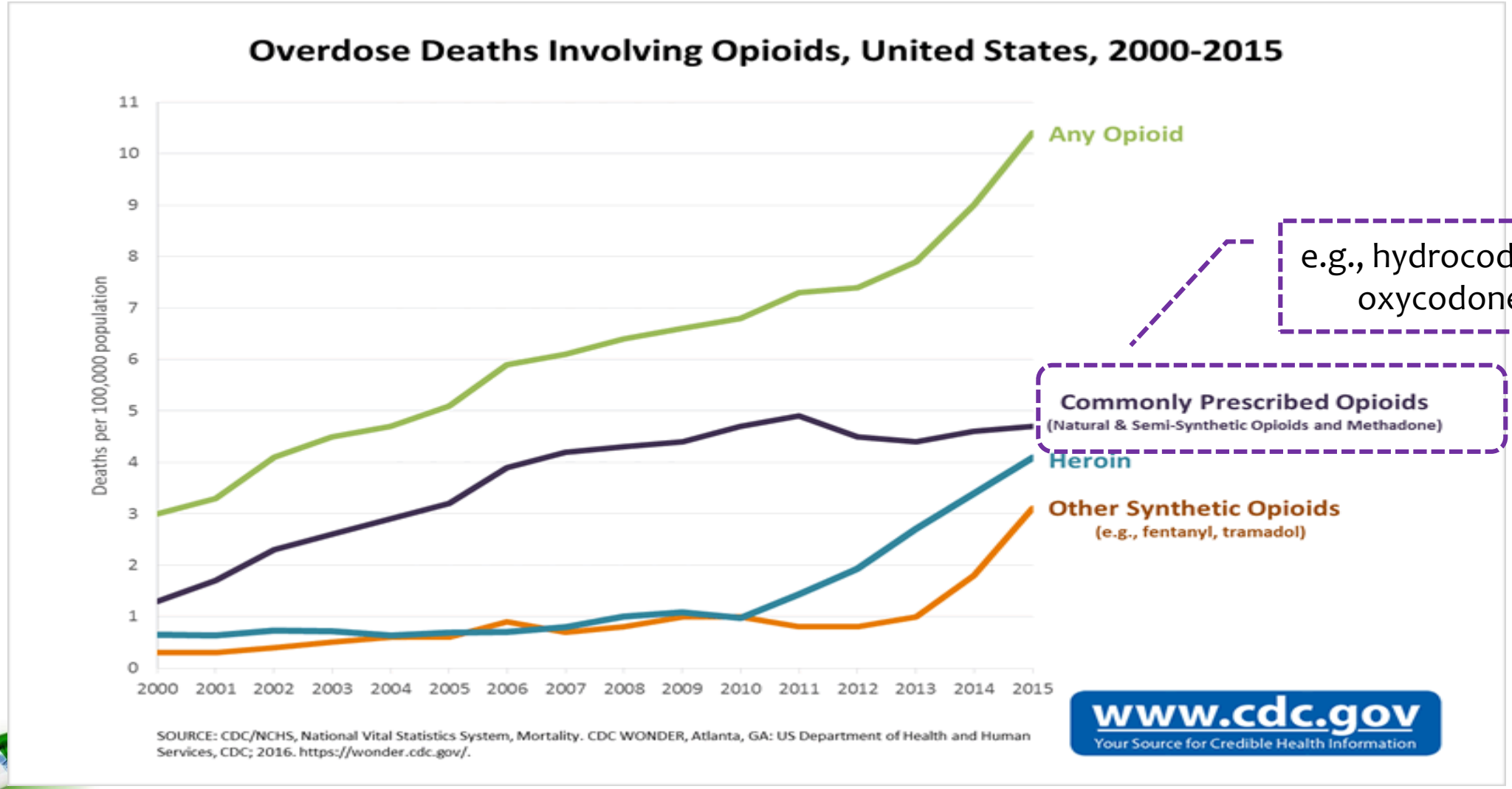
2010
Prescription opioids: 16,651 OD deaths
Heroin: 3,036 OD deaths

80-90% deemed UNINTENTIONAL

Data are from the National Vital Statistics System of the Centers for Disease Control and Prevention, the Treatment Episode Data Set of the Substance Abuse and Mental Health Services Administration, and the Automation of Reports and Consolidated Orders System of the Drug Enforcement Administration.

Volkow ND, et al. *N Engl J Med*. 2014;370(22):2063-6.
Jones CM, et al. *JAMA*. 2013;309(7):657-9.

Opioid Epidemic



Opioid Epidemic

Why?

It is estimated that almost 80% of opioid-related overdose deaths are considered accidental or unintentional

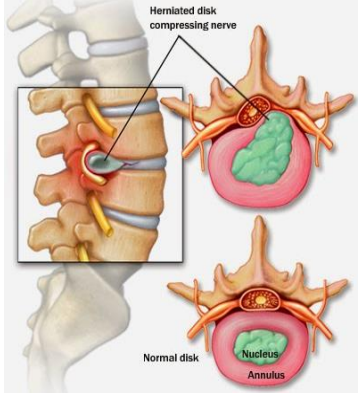
Due, in part, to
DRUG INTERACTIONS

SAMHSA. Available at: https://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf
Rudd RA. *MMWR Morb Mortal Wkly Rep*. 2016;64:1378-82.

Case Vignette Introduction

Opioid Pain Management Case

Background



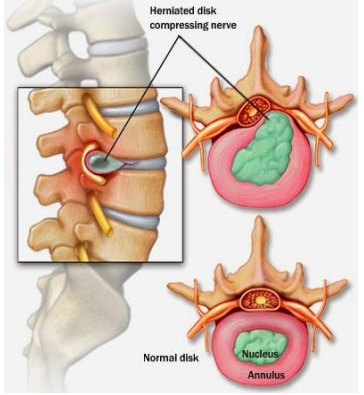
J.D. is a 54-year old male with post-surgical repair of spinal stenosis (L1-L2) following an injury.

His PMH includes Depression, HTN, and Asthma. He has NKDA.

Following surgery, he was started on tramadol by the pain management specialist

- Tramadol 50mg: Take 1 to 2 tablets every 4 to 6 hours as needed for pain

Opioid Pain Management Case
Background



During his follow-up visit with PCP approximately a week later, it was evident that he failed to achieve an adequate response and exhibited intolerable side effects with tramadol

- J.D. stated that he tried tramadol 50mg (i.e., 1 tablet) for 2 days but has been taking tramadol 100mg (i.e., 2 tablets) every 4 hours while awake for the past 5 days with only a small reduction in his pain intensity (7/10 at best)

- He also expressed that he has been experiencing nausea, constipation, and intermittent dizziness

Opioid Pain Management Case

Current Medication History

His PCP changes tramadol to hydrocodone/APAP

His current medication profile is as follows:

- Hydrocodone/acetaminophen 5/325 mg every 4 hours PRN pain – NEW
- Senna-S 2 tablets daily – NEW
- Sertraline 50 mg/day
- Metoprolol succinate 50 mg/day
- Hydrochlorothiazide 25 mg/day
- Beclomethasone 80 mcg/inhalation twice daily
- Albuterol MDI 2 puffs every 4 hours as needed

Unchanged

To Be Continued…

Opioid-Related Drug Interactions
Pharmacodynamic Mechanisms

Respiratory Depression & Sedation

In 2010, among overdose deaths involving opioids, the pharmaceuticals most often also involved in these deaths were benzodiazepines (30.1%; 5,017), antidepressants (13.4%; 2,239), and antipsychotics or neuroleptics (4.7%; 783)

Jones CM, et al. *JAMA*. 2013;309(7):657-9.

Respiratory Depression & Sedation

Four studies of fatal overdose deaths found evidence of concurrent benzodiazepine use in 30% to 60% of decedents

Jones CM, et al. *JAMA*. 2013;309:657-9.
Jones CM, et al. Am J Prev Med. 2015;49-493-501.
Dasgupta N, et al. Pain Med. 2016;17:85-98.
Gomes T, et al. Arch Intern Med. 2011;171:686-91.

Respiratory Depression

- Action-related (respiratory effects)
  - Concomitant administration with drugs that cause respiratory depression
    - Exemplar drugs that cause respiratory depression:
      - Benzodiazepines (e.g., Diazepam [Valium®])
  - Use of opioids in patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve
    - COPD, cor pulmonale, morbid obesity

Sedation

- Action-related (CNS effects)
  - Concomitant administration with drugs that cause CNS depression
    - Exemplar drugs that cause CNS depression:
      - Benzodiazepine receptor agonists (e.g., diazepam ([Valium®])
      - Tricyclic antidepressants (e.g., amitriptyline [Elavil®])
      - Antipsychotics / Neuroleptics (e.g., quetiapine [Seroquel®])

Opioid-Related Drug Interactions
Pharmacokinetic Mechanisms

Opioid Metabolic Pathways

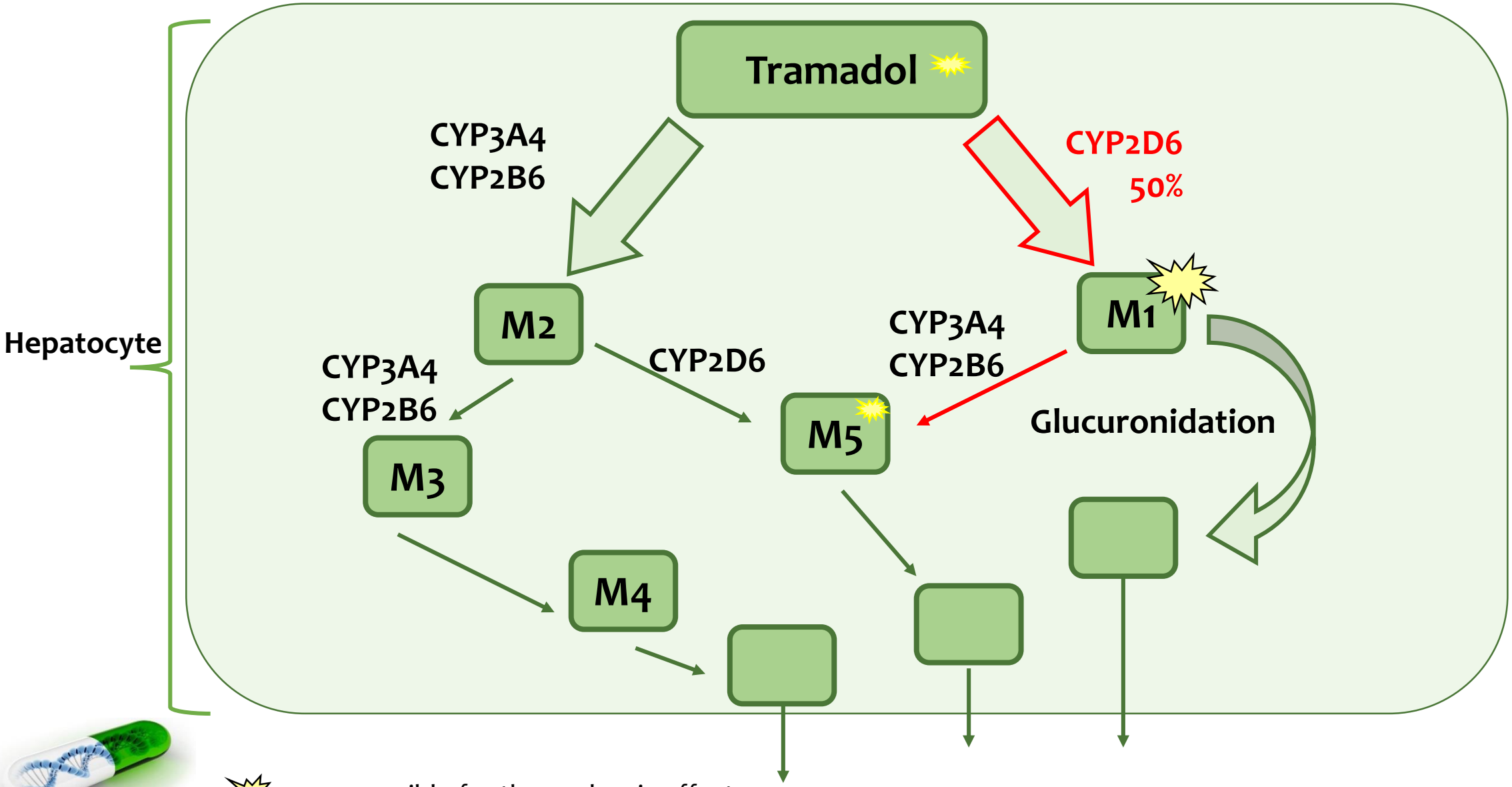
Opioid Metabolism

Strong | Moderate | Weak

Opioid	CYP2D6	CYP3A4	CYP2B6
Codeine	5%*	10%	
Morphine	NON P450		
Tramadol	50%*	10%	10%
Oxycodone	15%*	30%	
Oxymorphone	NON P450		
Hydrocodone	10%*	55%	
Hydromorphone	NON P450		
Fentanyl		90%	
Methadone	10%		50%
Tapentadol	25%		
Dihydrocodeine	25%		

* = Pro-drug or drug that is converted to a more active metabolite

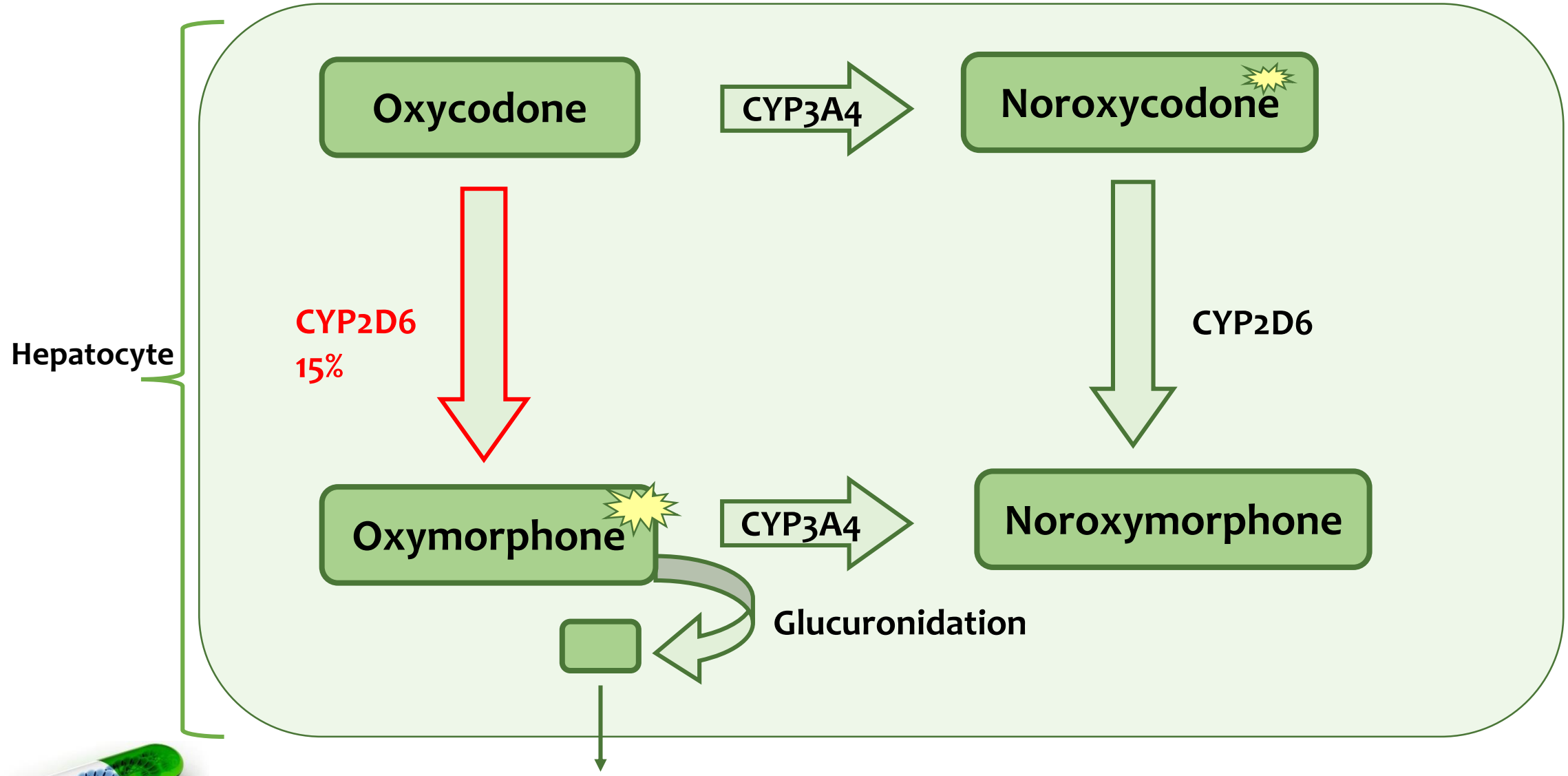
Tramadol Metabolic Pathway



= responsible for the analgesic effect

Gong L. *Pharmacogenet Genomics*. 2014;24:374-80.

Oxycodone Metabolic Pathway



= responsible for the analgesic effect

Smith HS. *Mayo Clinic Proceedings*. 2009;84:613-24.

Drug-Drug Interaction Examples

Opioid Pharmacokinetic Interaction

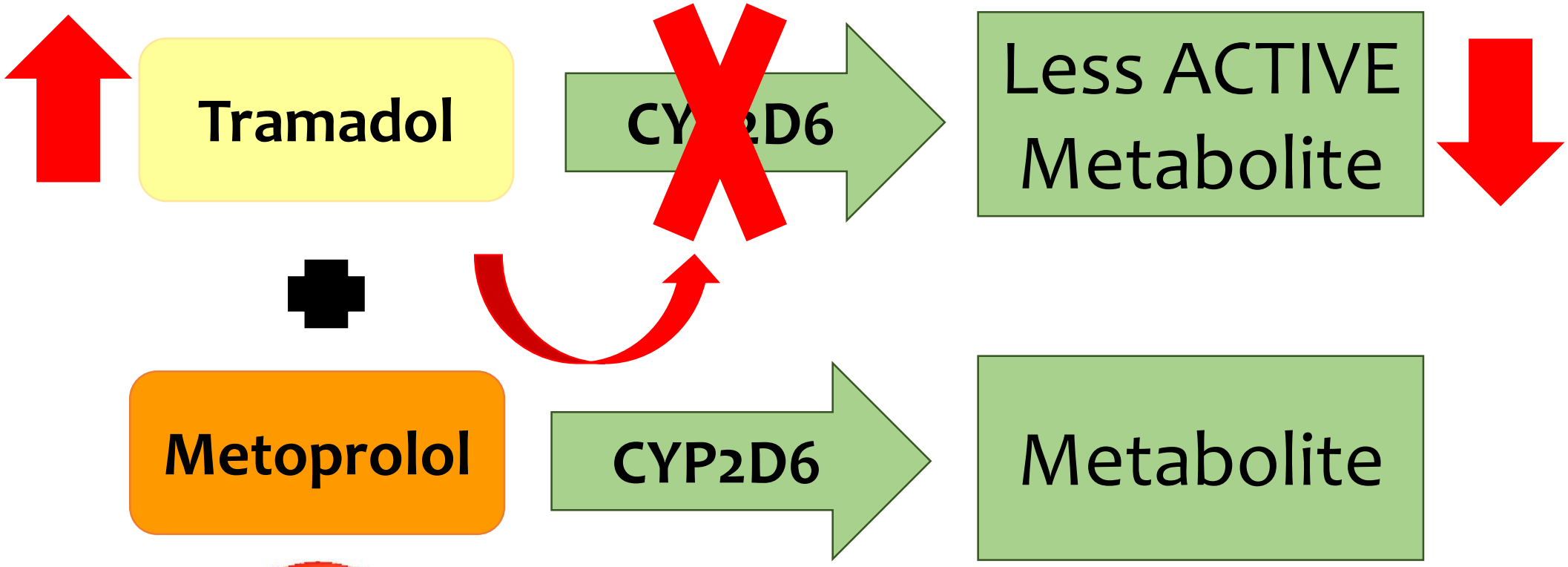
Competitive Inhibition

Tramadol → **CYP2D6** → ACTIVE Metabolite

Expected (normal) analgesic response

Opioid Pharmacokinetic Interaction

Competitive Inhibition



Reduced analgesic response

Opioid Pharmacokinetic Interaction

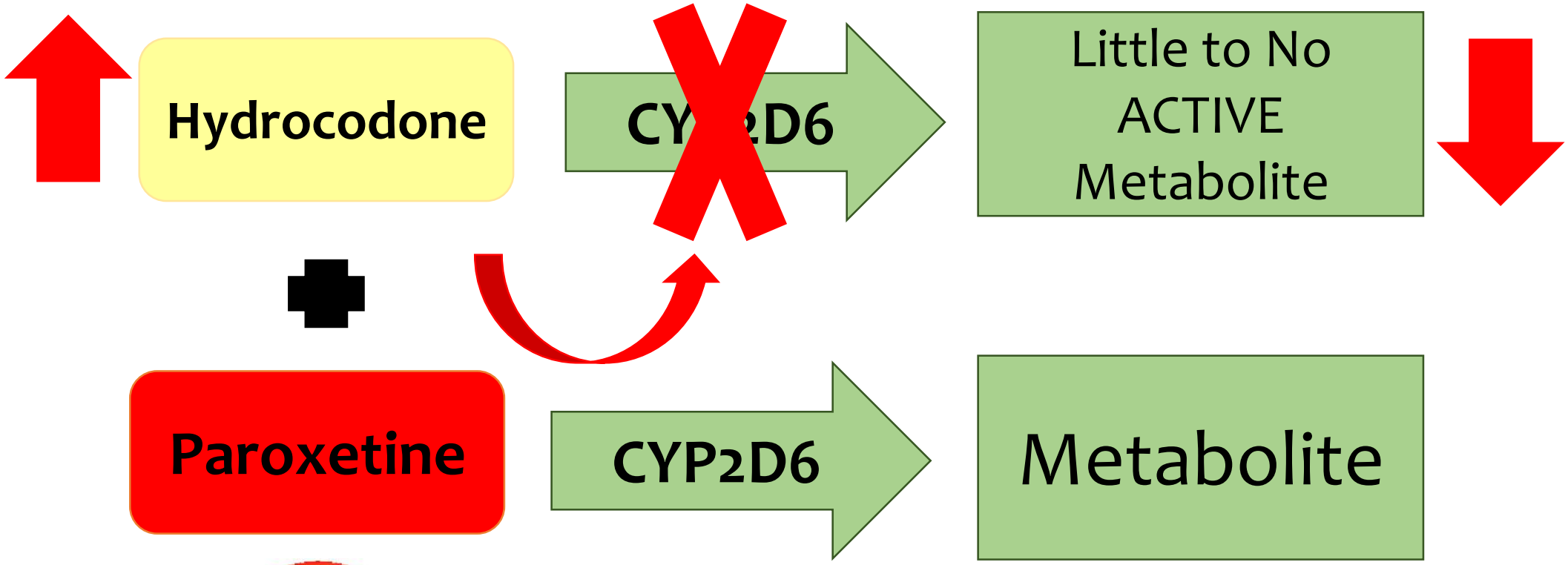
Non-Competitive Inhibition

Hydrocodone → **CYP2D6** → ACTIVE Metabolite

Expected (normal) analgesic response

Opioid Pharmacokinetic Interaction

Non-Competitive Inhibition



Reduced analgesic response

Opioid-Related Drug Interactions Pharmacogenomic (PGx) Mechanisms

How genetic variations affect drug disposition & response

Opioids

The CYP450 enzymes are under genetic control

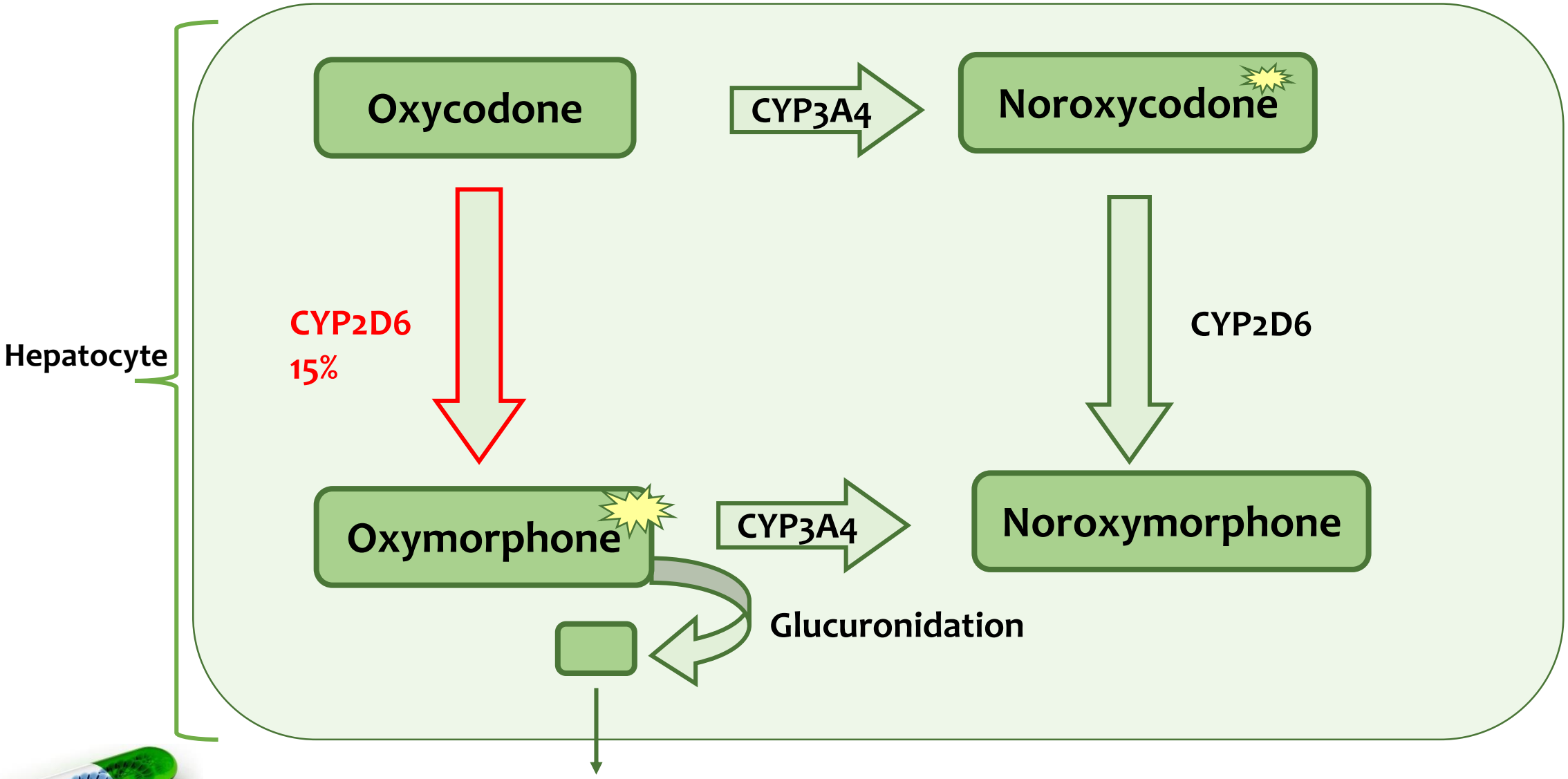
Opioid	CYP2D6	CYP3A4	CYP2B6
Codeine	5%*	10%	
Morphine	NON P450		
Tramadol	50%*	10%	10%
Oxycodone	15%*	30%	
Oxymorphone	NON P450		
Hydrocodone	10%*	55%	
Hydromorphone	NON P450		
Fentanyl		90%	
Methadone	10%		50%
Tapentadol	25%		
Dihydrocodeine	25%		

* = Pro-drug or drug that is converted to a more active metabolite

Drug-Gene Interaction Examples

Clinical Relevance Citations:
Poulsen L. *Eur J Clin Pharmacol*. 1996;51:289-95.
Gasche Y. *N Engl J Med*. 2004;351:2827-31.
Ciszkowski C. *N Engl J Med*. 2009;361:827-8.
Argoff CE. *Clin J Pain*. 2010;26:S16-S20.
Lurcott G. *Anesth Prog*. 1998;45:154-6.

Oxycodone Metabolic Pathway



= responsible for the analgesic effect

Smith HS. *Mayo Clinic Proceedings*. 2009;84:613-24.

Oxycodone Response

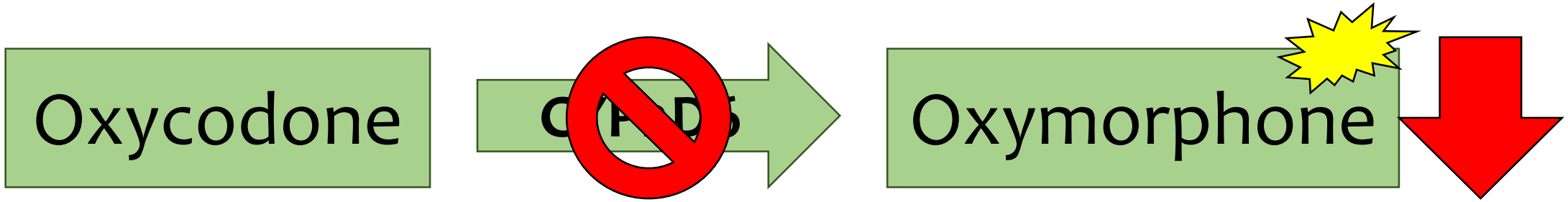
Normal Response

Oxycodone → **CYP2D6** → Oxymorphone

CYP2D6 *1/*1
Normal Metabolizer (NM)

Oxycodone Response

Reduced or No Response



CYP2D6 *4/*4
Poor Metabolizer (PM)

A CYP2D6 poor metabolizer does not metabolize CYP2D6 substrates (e.g., opioids) and, therefore, has greater than expected exposure to the parent drug & lower than expected or no exposure to active metabolites

Giving oxycodone to patients without CYP2D6 activity can be like giving a placebo

Oxycodone Response

Enhanced Response

Oxycodone

CYP2D6

CYP2D6

CYP2D6

Oxymorphone

CYP2D6 *1/*1x2
Ultra-rapid Metabolizer (UM)

Oxycodone Response

Altered Response – Phenoconversion

CYP2D6 *1/*1
Normal Metabolizer (NM)

Oxycodone → **CYP2D6** → Oxymorphone ↓

Bupropion → **CYP2D6**

This can be mitigated by giving Oxycodone 2-4 hours **prior** to Bupropion

CYP2D6 behaves like an Intermediate Metabolizer (IM) or Poor Metabolizer (PM)

Oxycodone Response

Altered Response – Phenoconversion

CYP2D6 *1/*1
Normal Metabolizer (NM)

Oxycodone

CYP2D6

Oxymorphone

Amiodarone

This can NOT be mitigated by changing time of administration

CYP2D6 behaves like
Poor Metabolizer (PM)

Case Vignette Revisited

Opioid Pain Management Case
Explained – Tramadol

Metoprolol (moderate substrate) is blocking the metabolism of Tramadol (weak substrate)
As a result, Tramadol cannot be activated to its more potent metabolite

Opioid Pain Management Case
Continued

Following his PCP visit, J.D. begins taking the hydrocodone/acetaminophen 5/325 mg as prescribed

After several days, he calls his PCP to report that this pain medication does not seem to be helping much more than the tramadol

His PCP writes a new prescription for hydrocodone/acetaminophen 10/325 mg every 4 to 6 hours PRN pain

What should we expect?

Opioid Pain Management Case
Explained – Hydrocodone

The result is expected to be the SAME

Opioid Pain Management Case

Scenario 1

J.D. continues taking the hydrocodone/acetaminophen 10/325 mg as prescribed, with mild to modest analgesic response

- Takes 1 tablet 4-5 times per day
- Best 4-5/10 pain score on Likert scale
- Most improvement at night

After several days, he calls his PCP to report that his analgesic response, and reports that his nausea & constipation is mitigated & his dizziness has improved

Unsuspecting of a drug-drug interaction, his PCP orders a PGx test to determine his CYP2D6 genotype-phenotype status

- His result comes back as follows: CYP2D6*1/*1 – normal metabolizer (NM)

What should we expect?

Opioid Pain Management Case
Explained – Hydrocodone

Metoprolol is causing phenoconversion of the CYP2D6 isoenzyme from NM to IM or PM
As a result, Hydrocodone cannot be activated to its more potent metabolite (hydromorphone)

Opioid Pain Management Case
Explained – Hydrocodone

The result is expected to be the SAME

Opioid Pain Management Case

Scenario 2

Unimpressed with the PGx test result, about a week later, the PCP decides to change J.D. from hydrocodone/acetaminophen to oxycodone

- Oxycodone extended-release 10 mg twice daily (every 12 hours)
- Oxycodone immediate-release 5 mg every 4 to 6 hours PRN breakthrough pain

The PCP also adds pregabalin for potential nerve pain

- Pregabalin 50 mg at bedtime x 3 days then 50 mg twice daily

J.D. begins taking his new prescriptions the following day

What should we expect?

Opioid Pain Management Case
Explained – Oxycodone

Metoprolol is still competitively inhibiting the opioid & causing phenoconversion
As a result, Oxycodone cannot be activated to its more potent metabolite (oxymorphone)

Opioid Pain Management Case
Explained – Oxycodone

The result is expected to be the SAME

To Be Continued…

Case Vignette
Attempts at Mitigating Strategies

Opioid Pain Management Case

Scenario 3

A week and a half later, J.D. calls his PCP to report that his pain control is relatively unchanged & that he tried taking the pregabalin twice daily but could not tolerate it because of fogginess & daytime sleepiness

After consulting with the pharmacist that rotates in his practice, the PCP recognizes that J.D. is suffering from multiple drug interactions

- Oxycodone & pregabalin – sedation
- Oxycodone & metoprolol – competitive inhibition & phenoconversion

He also realizes that J.D. has become physically & possibly psychologically addicted to opioids

The PCP decides to stop the pregabalin and switch the metoprolol to atenolol

- Atenolol 50 mg/day

What should we expect?

Opioid Pain Management Case
Explained – Oxycodone

Atenolol does NOT competitively inhibit the opioid
As a result, Oxycodone CAN be activated to its more potent metabolite (oxymorphone)

Opioid Pain Management Case
Explained – Oxycodone

We should expect a potential overdose

To Be Continued…

Opioid Pain Management Case

Scenario 4

Several days after changing from metoprolol to atenolol, J.D.'s wife calls 9-11

- She found J.D. slumped over in his chair and difficult to arouse

J.D. is brought to the emergency department for urgent care

What could have been done differently?

Opioid Pain Management Case
Scenario 4 (cont.)

What could have been done differently?

When changing to atenolol, the PCP should have reduced the oxycodone dosage

Why?

- J.D. was not fully metabolizing the previous opioids and, therefore, the concentrations were lower than expected
- However, when the competitive inhibition was mitigated, the opioid concentrations rose, and this occurred over several days (due to relatively high bioavailability of oxycodone)

Opioid Pain Management Case
Scenario 4 (cont.)

What could have been done differently?

Instead of changing metoprolol to atenolol, the PCP could have changed the oxycodone to morphine or oxymorphone

Why?

- These opioids do not undergo metabolism by the CYP2D6 isoenzyme
- In doing so, still, the estimated conversion should be significantly reduced (50-75%) to account for incomplete cross-tolerance (i.e., treat J.D. like he is opioid naïve)

Improving Opioid Prescribing
Mitigating Strategies

Pharmacodynamic Interactions

Mitigating Pharmacodynamic Interactions

- Avoid concomitant use of opioids with other drugs that can depress / suppress the respiratory system
  - Especially in patients with compromised pulmonary function
- Avoid concomitant use of opioids with other CNS-depressing drugs
- Always monitor
  - Medication adherence (use, misuse) & abuse
  - Physical examination & toxicology

Mitigating Pharmacodynamic Interactions

- Use lowest effective doses & shortest durations necessary
- Taper opioids & most other drugs slowly
  - Regular trial of dosage reduction and/or discontinuation
  - Monitor effects & adverse effects
- Have naloxone (Narcan®) available for use in case of emergency

Pharmacokinetic Interactions

Mitigating Pharmacokinetic Interactions

- Affinity principle
  - Drug with the highest affinity wins over drug(s) with lower affinity
    - Higher affinity substrate: causes the interaction (i.e., "perpetrator")
    - Lower affinity substrate: suffers from the interaction (i.e., "victim")

- Separate the times of administration

  - Rule of thumb: Give the lower affinity drug (e.g., CYP2D6 opioid) 2 to 4 hours before the higher affinity competing substrate(s)
    - Substrate with the lower affinity can bind to the enzyme unoccupied by the higher affinity substrate & be metabolized
    - Thus, the *magnitude* of the interaction will be significantly reduced

  - This strategy does not work for non-competitive inhibition

Mitigating Pharmacokinetic Interactions

- Change the opioid (i.e., "victim" drug)
  - Use an opioid that is not primarily metabolized by the CYP2D6 enzyme
    - Examples: morphine, oxymorphone, methadone
  - Use equianalgesic dosing tables for guidance
  - Empirically reduce (e.g., 25%) the alternative opioid dosage
  - Start low & go slow (i.e., treat as opioid naïve)

- Change the competing drug (i.e., "perpetrator" drug)
  - Must empirically reduce the opioid dosage to avoid OD

Pharmacogenomic Interactions

Mitigating Pharmacogenomic Interactions

- Individualize drug therapy
  - Select an opioid based on genetic results
  - Choose concomitant drugs based on genetic results
- Avoid phenoconversion
  - Do not “jam up” metabolic pathways
- Use caution & adjust appropriately when changing drugs
  - Example: Changing or discontinuing a drug causing phenoconversion for the opioid could result in an OD – adjust dosage accordingly

Opioid-Related Drug Interactions
Closing

Summary

- The CYP2D6 enzyme is responsible for metabolizing many commonly used opioids to more active metabolites
  - These opioids are weak substrates and, therefore, can be competitively inhibited by moderate to strong substrates (e.g., antidepressants)
  - This will result in reduced analgesic effect and potentially side effects
  - Clinically, we tend to increase the opioid dosage to improve analgesic effect, which may result in opioid addiction, misuse, and/or abuse

- The CYP2D6 enzyme also is highly polymorphic
  - Genetic variations and drug-gene interactions resulting in phenoconversion can significantly alter opioid response as well

Summary

- Drug interactions involving opioids are a key upstream driver of the opioid epidemic

- Mitigating strategies are multifaceted & require careful consideration of the nature & extent of multi-drug interactions

Discussion

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