Non-CME Webinar Series
designed with the trainee in mind
first Tuesday of the month

ASRA PAIN MEDICINE
THE ASSOCIATION OF PAIN PROGRAM DIRECTORS

Opioid Metabolism

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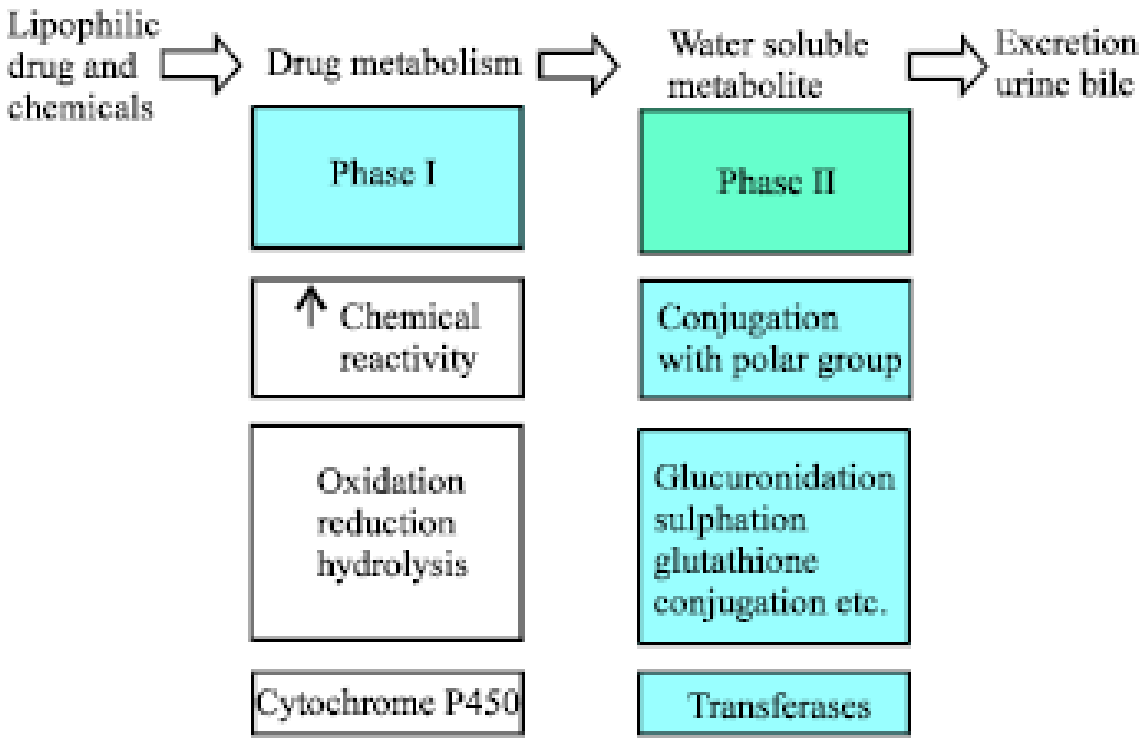
Outline

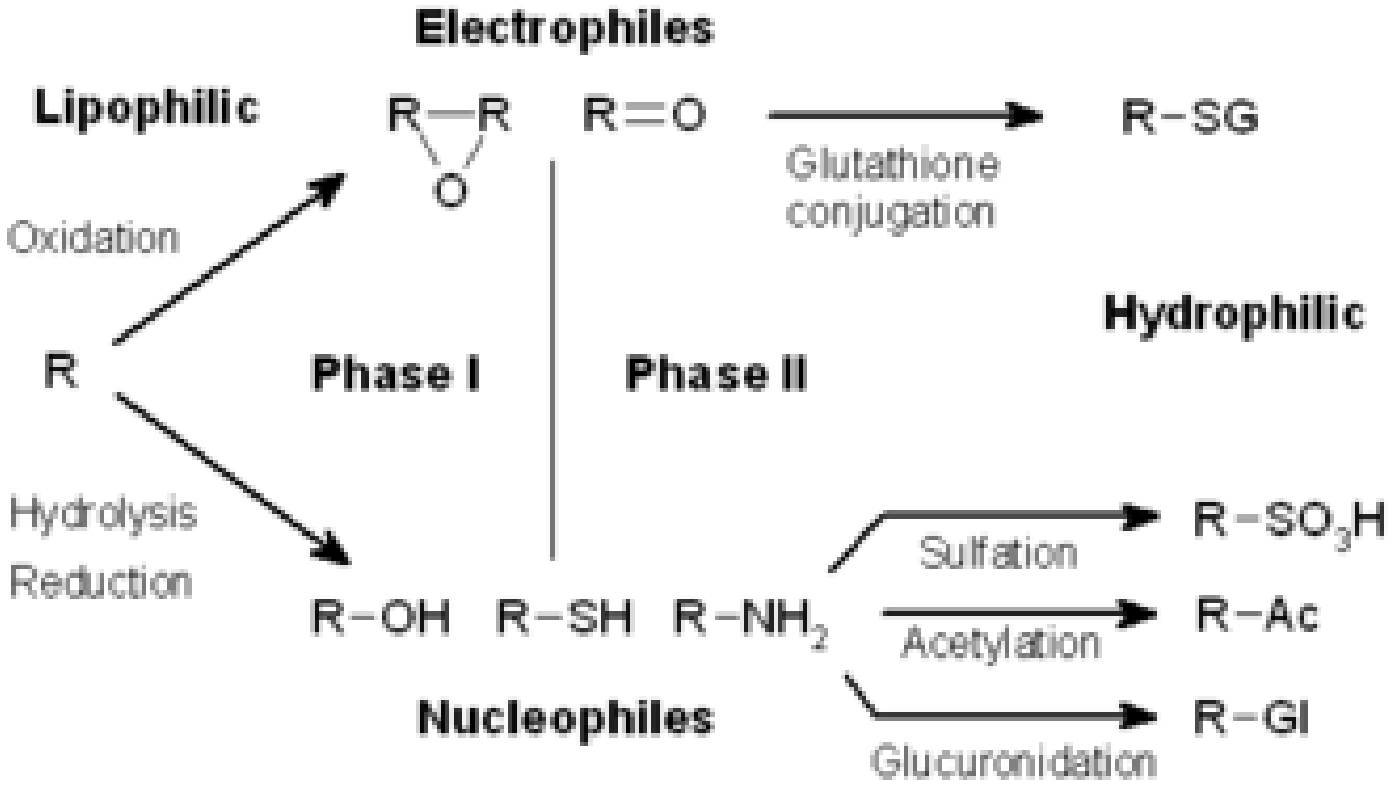
- Phases of Drug Metabolism
  - Cyt P450 system
- Opioid Chemical Structure
- Opioid Metabolism
  - Morphine
  - Codeine
  - Hydrocodone/Hydromorphone
  - Oxycodone/Oxymorphone
  - Methadone
  - Fentanyl
  - Tramadol
  - Buprenorphine
- Recap of Metabolism
- Activating and Inactivating Cytochrome P450 factors

Phases of Drug Metabolism

- Phase 1
  - Oxidation
  - Reduction
  - Hydrolysis
- Phase 2
  - Conjugation
    - Glucuronidation
    - Acetylation
    - Sulphation
    - Amidation



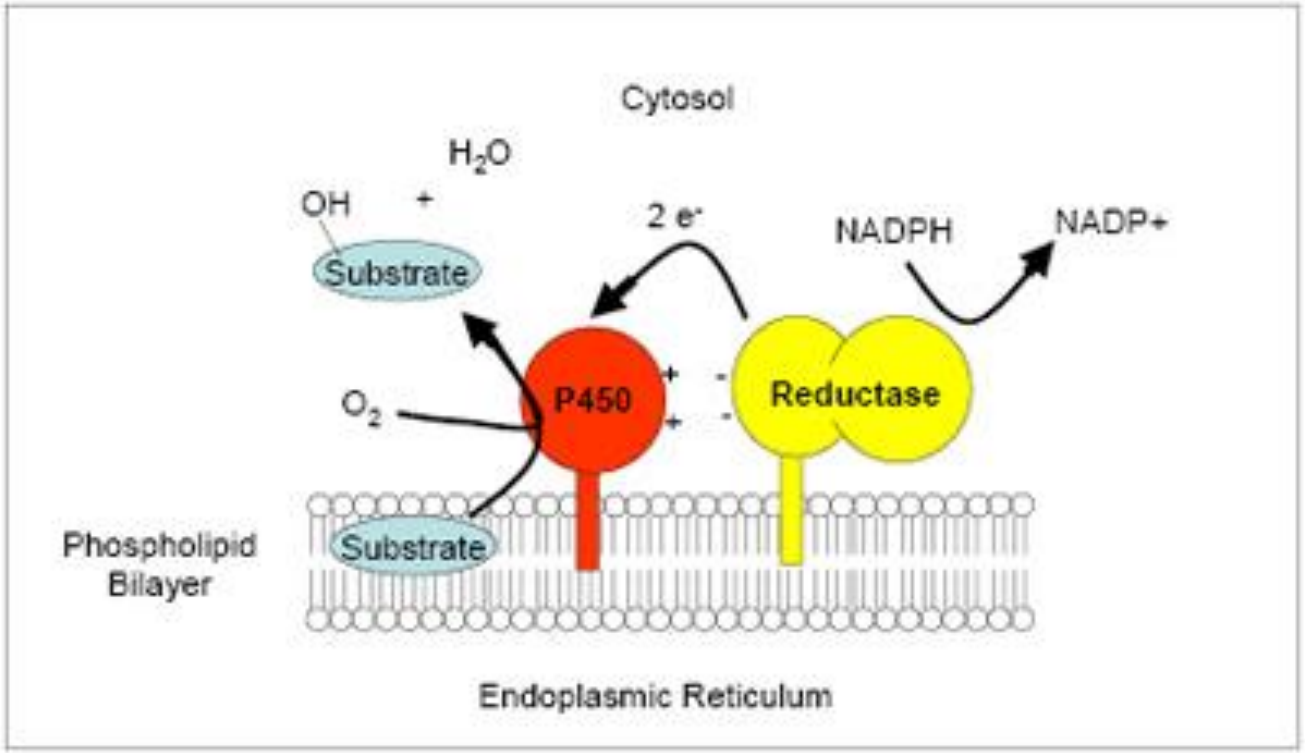
Phases of Drug Metabolism



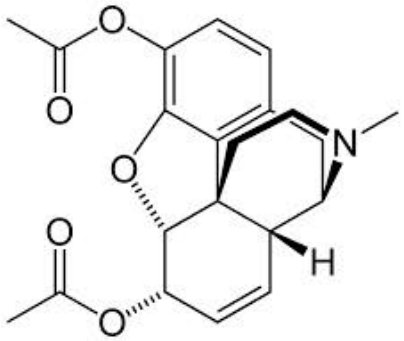
Cytochrome P450 System

- Cytochromes P450 (CYPs) belong to the superfamily of proteins containing a heme cofactor and, therefore, are hemoproteins. CYPs use a variety of small and large molecules as substrates in enzymatic reactions. They are, in general, the terminal oxidase enzymes in electron transfer chains, broadly categorized as P450-containing systems.
- CYPs are the major enzymes involved in drug metabolism, accounting for about 75% of the total metabolism.[16] Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
- Account for most opioid metabolism

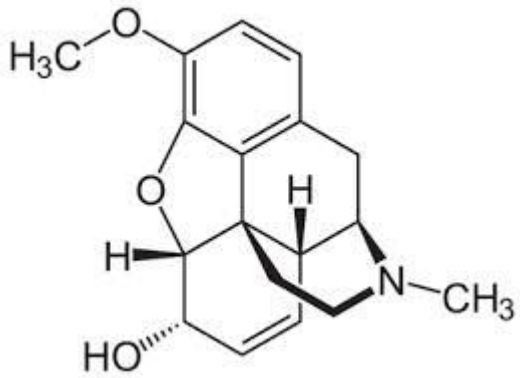
Cytochrome P450 System



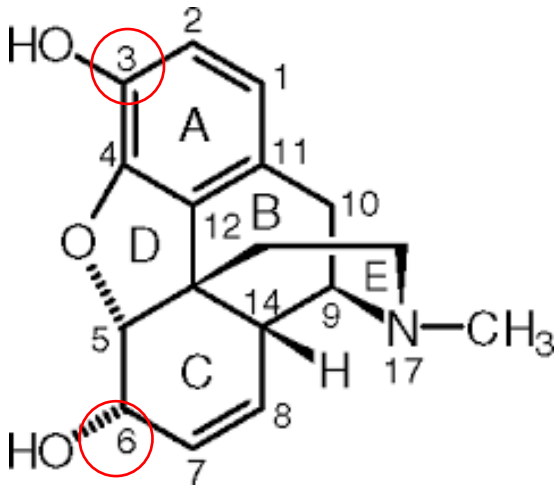
Opiate Chemical Structure



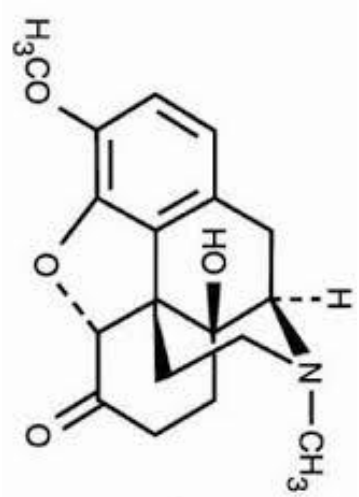
Heroine



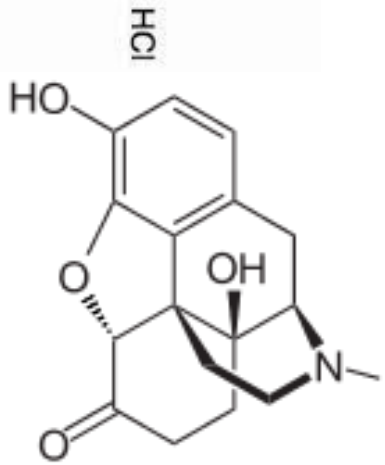
Codeine



Morphine



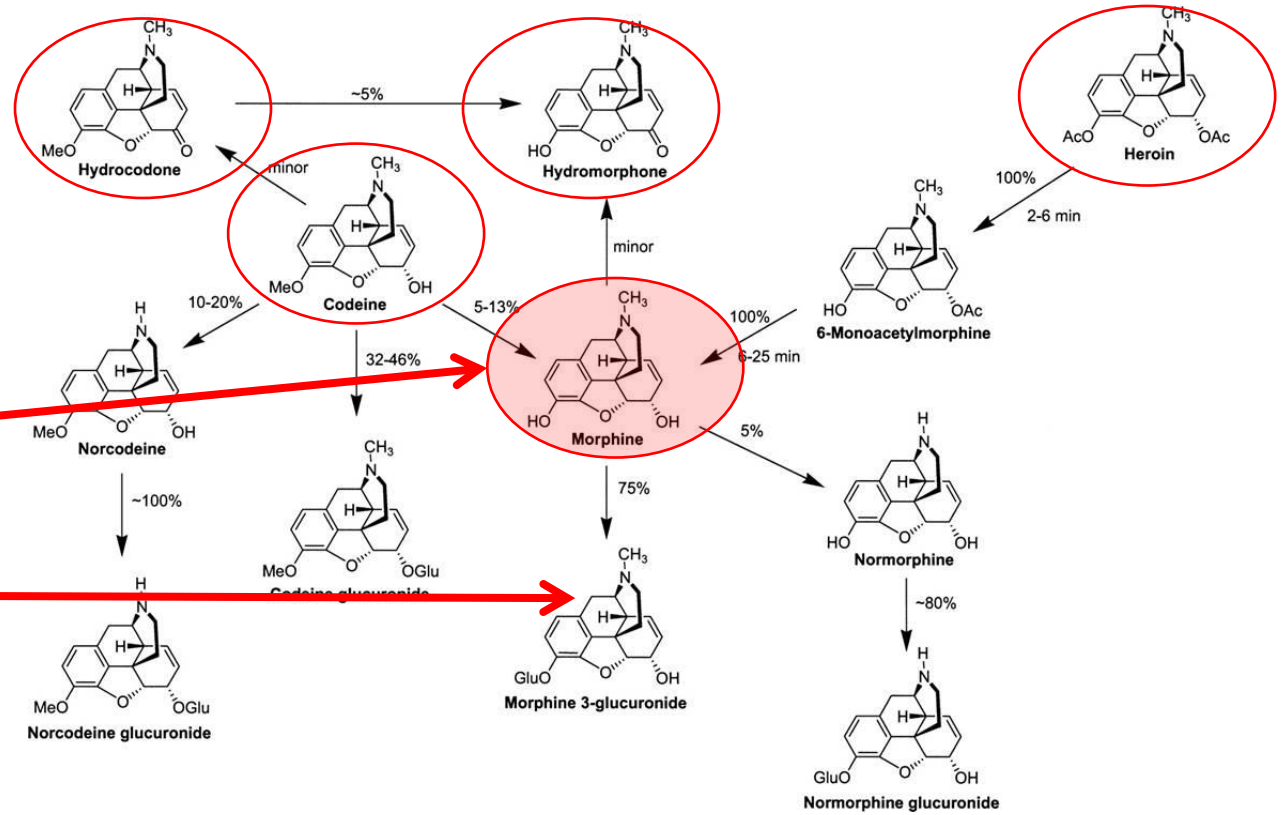
Oxycodone



Oxymorphone

Overview of Opiate Metabolism

- **Most roads lead to Morphine**
- **Beware of Opiate side effects due to decreased elimination of active drug and metabolites**
  - **Respiratory depression**
  - **Hypotension**
  - **CNS Toxicity (lethargy, somnolence, confusion)**
  - **Nausea and Vomiting**



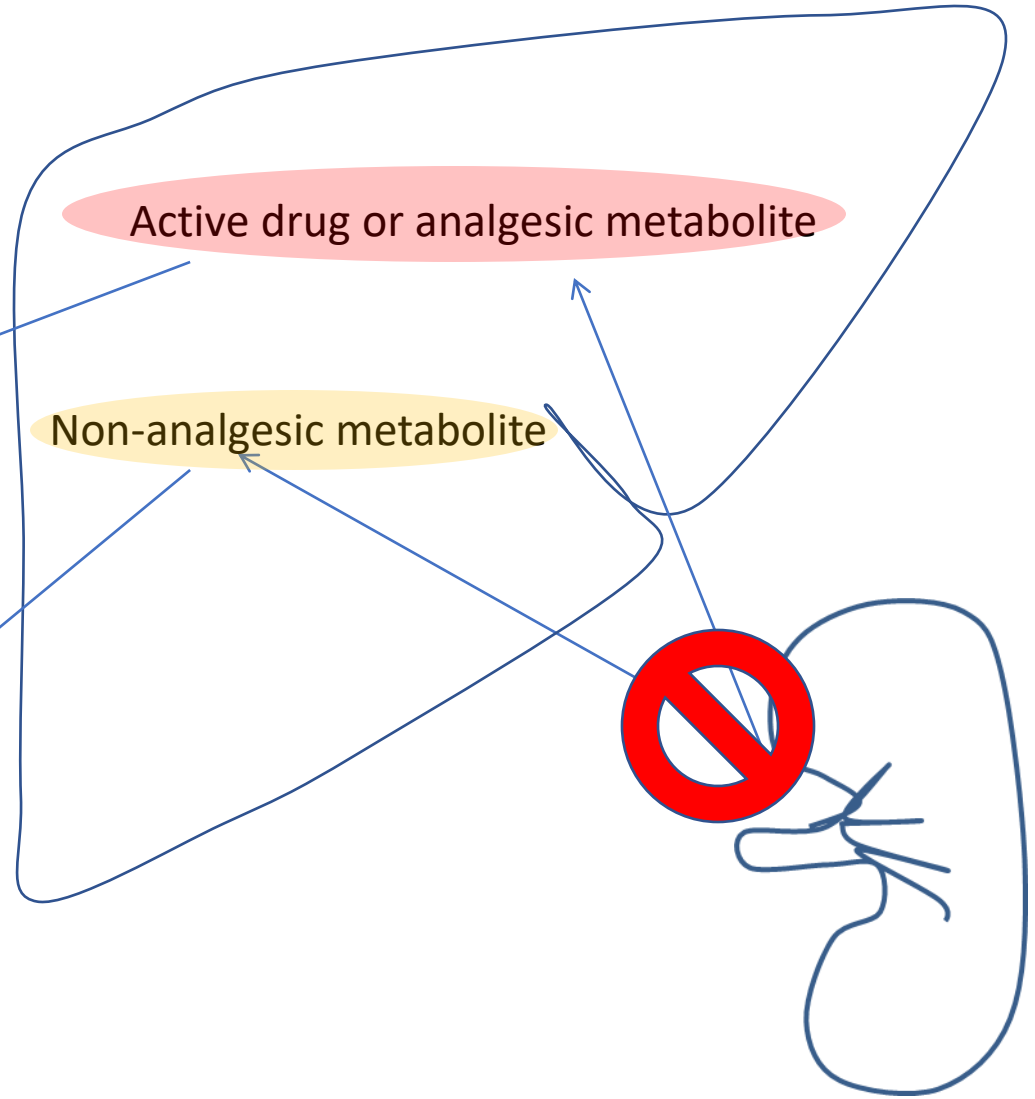
Overview of Opiate Metabolism

•Decreased excretion of active drug metabolite may cause symptoms of opiate toxicity:

- **•Lethargy**
- **•Somnolence**
- **•Respiratory distress**

•Decreased excretion of inactive metabolite may cause:

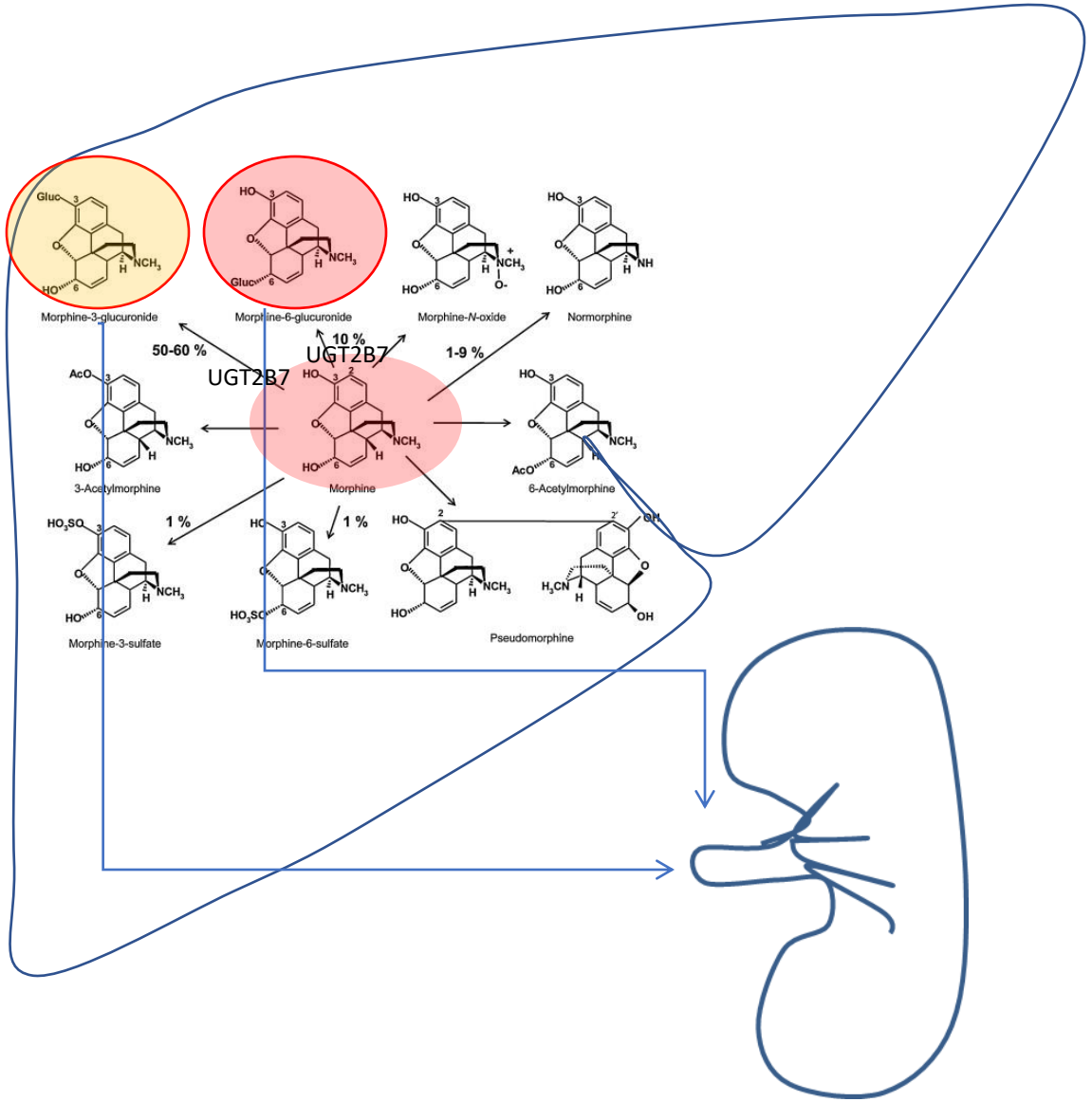
- **•Neuroexcitability (myoclonus, irritability, allodynia)**
- **•Nausea**
- **•Abdominal pain**



*Color coding will be used for upcoming diagrams

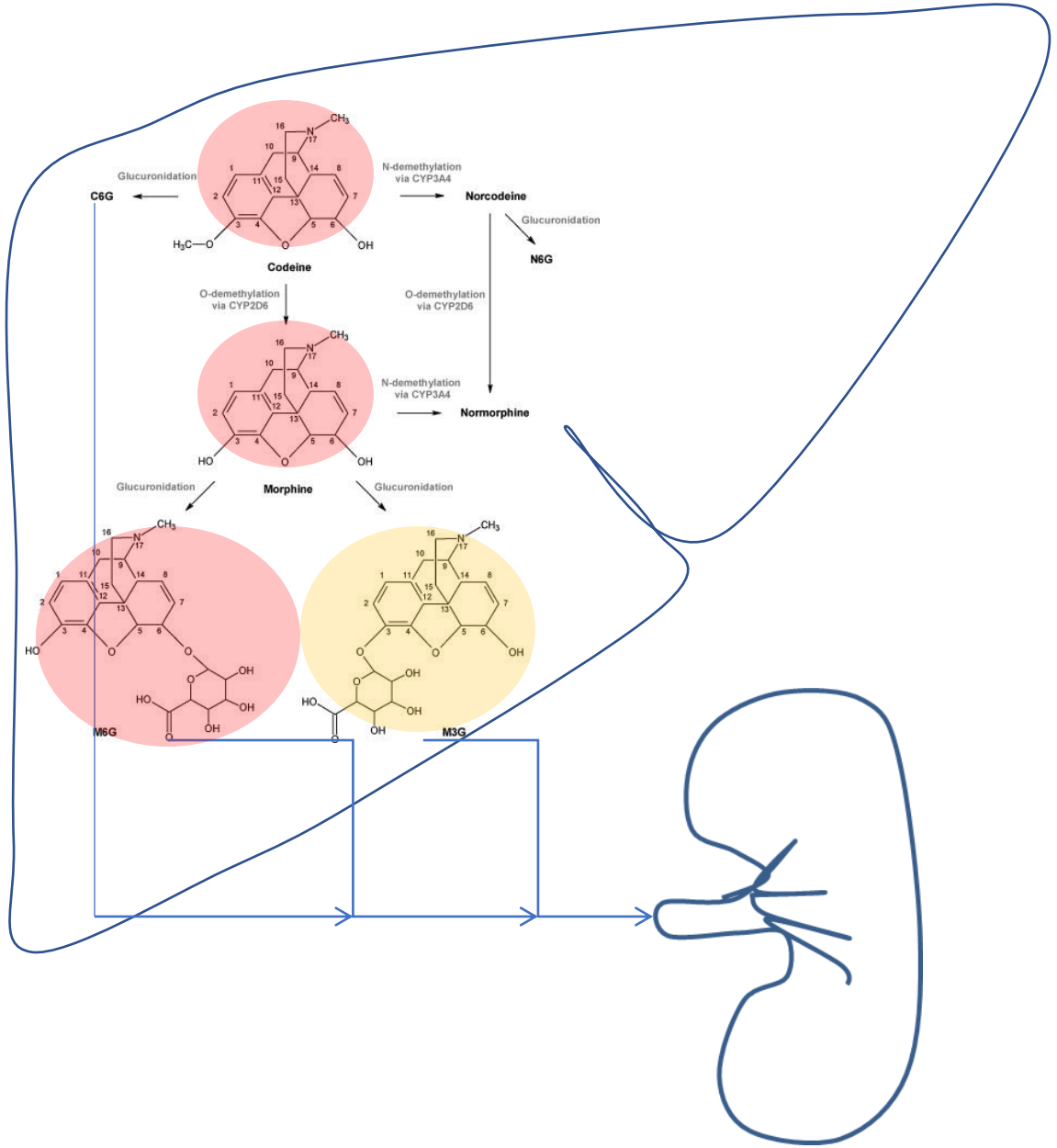
Morphine

- Morphine is metabolized to M3G and M6G in the liver.
  - Has slow diffusion our of the CNS
  - **M6G is the active metabolite and has high mu receptor binding affinity**
  - **M3G is an inactive metabolite which has low mu receptor binding, antagonizes M6G binding, and can cause CNS excitation**



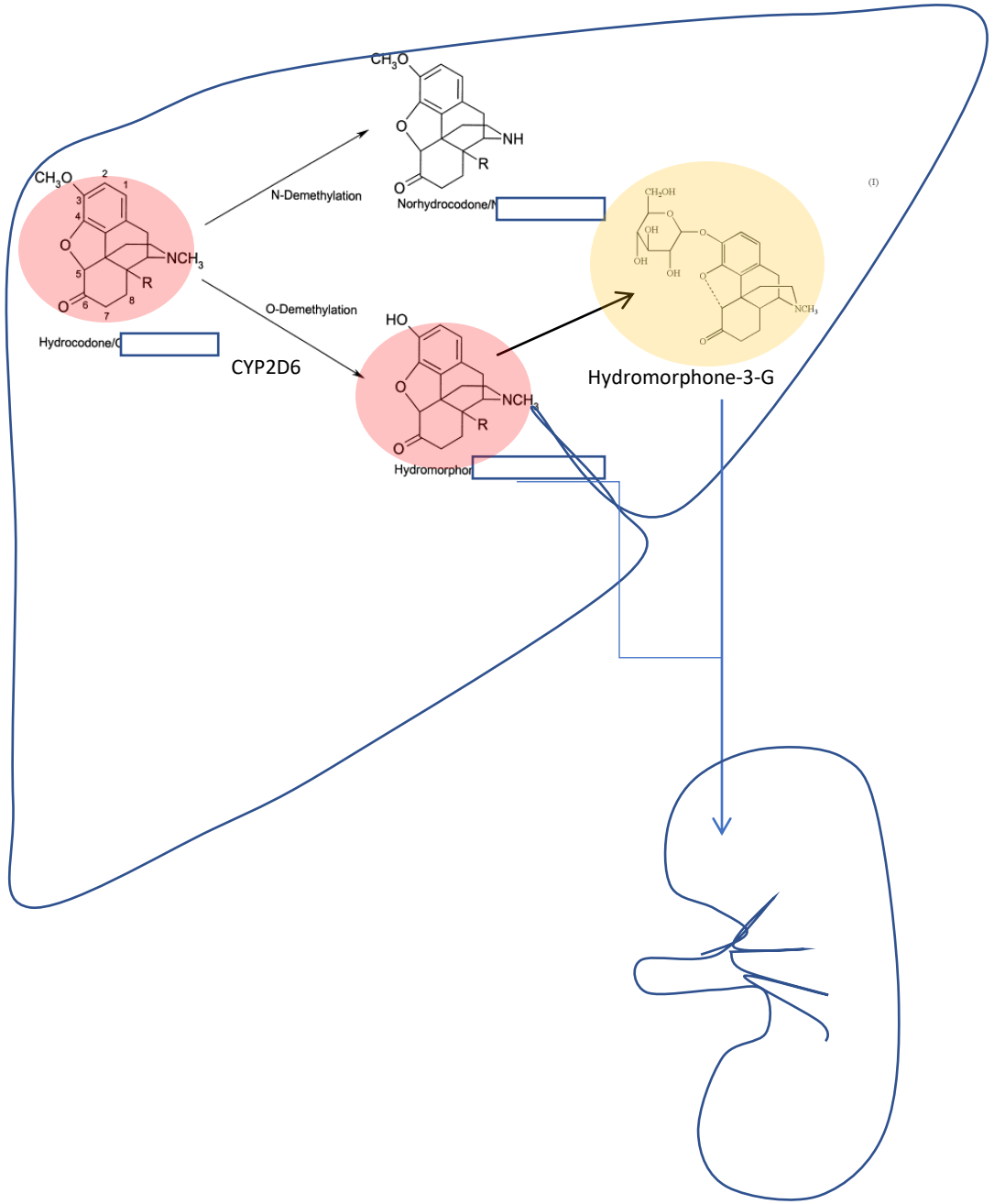
Codeine

- Codeine is metabolized by CYP2D6 to Codeine-6-G (81%) and Morphine (10%)
- Codeine and metabolites are renally excreted, therefore **must be cautious of morphine and M-6-G intoxication (lethargy, decreased respiration) in CKD**



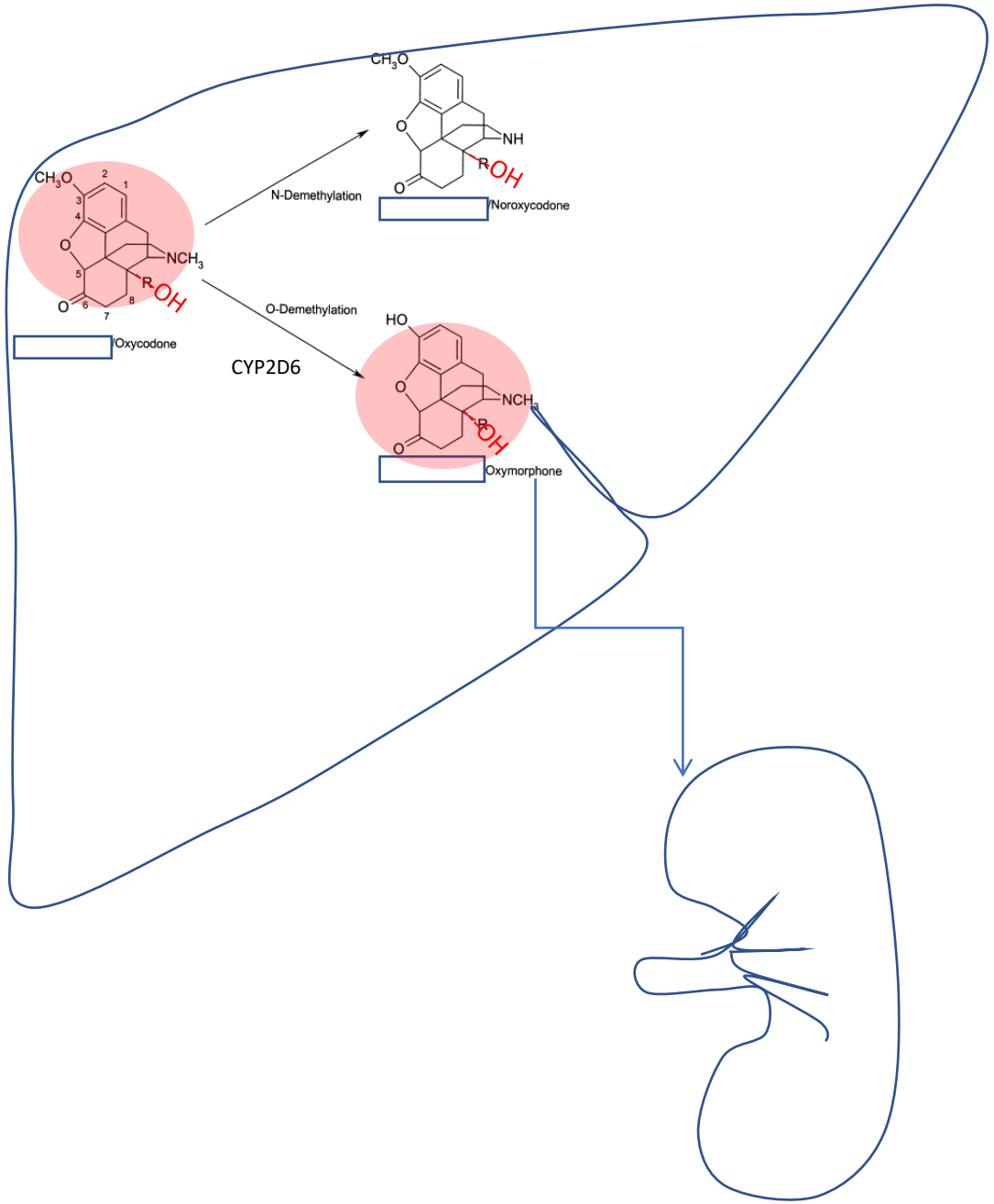
Hydrocodone and Hydromorphone

- **Hydrocodone metabolized to Hydromorphone in the liver by CYP2D6**.
  - Poor metabolizers experience little to no analgesia.
- Hydromorphone is metabolized to Hydromorphone-3-G in the liver.
  - 40% is renally excreted
  - **Hydromorphone-3-G has no analgesic activity, but can cause aggitation, confusion, and hallucinations**



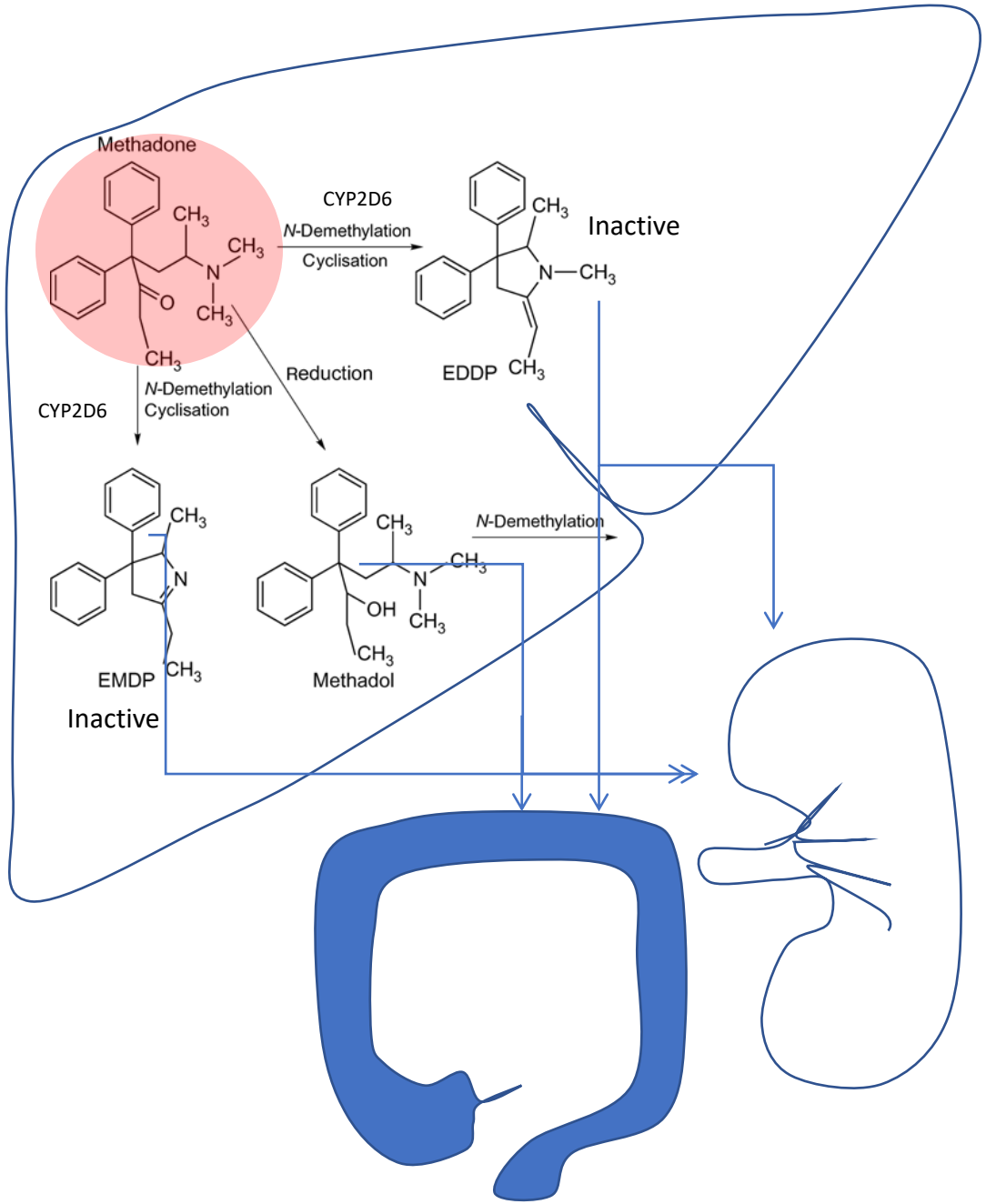
Oxycodone and Oxymorphone

- **Oxycodone metabolized to Oxyomorphone in the liver by CYP2D6.**
  - Poor metabolizers will experience little or no analgesia
  - Oxymorphone is the only active metabolite of oxycodone
  - Elimination half life is impaired in CKD and excretion of metabolites is impaired
- CNS toxicity and sedation with usual doses oxycodone in CKD have been published (Fitzgerald 1991)



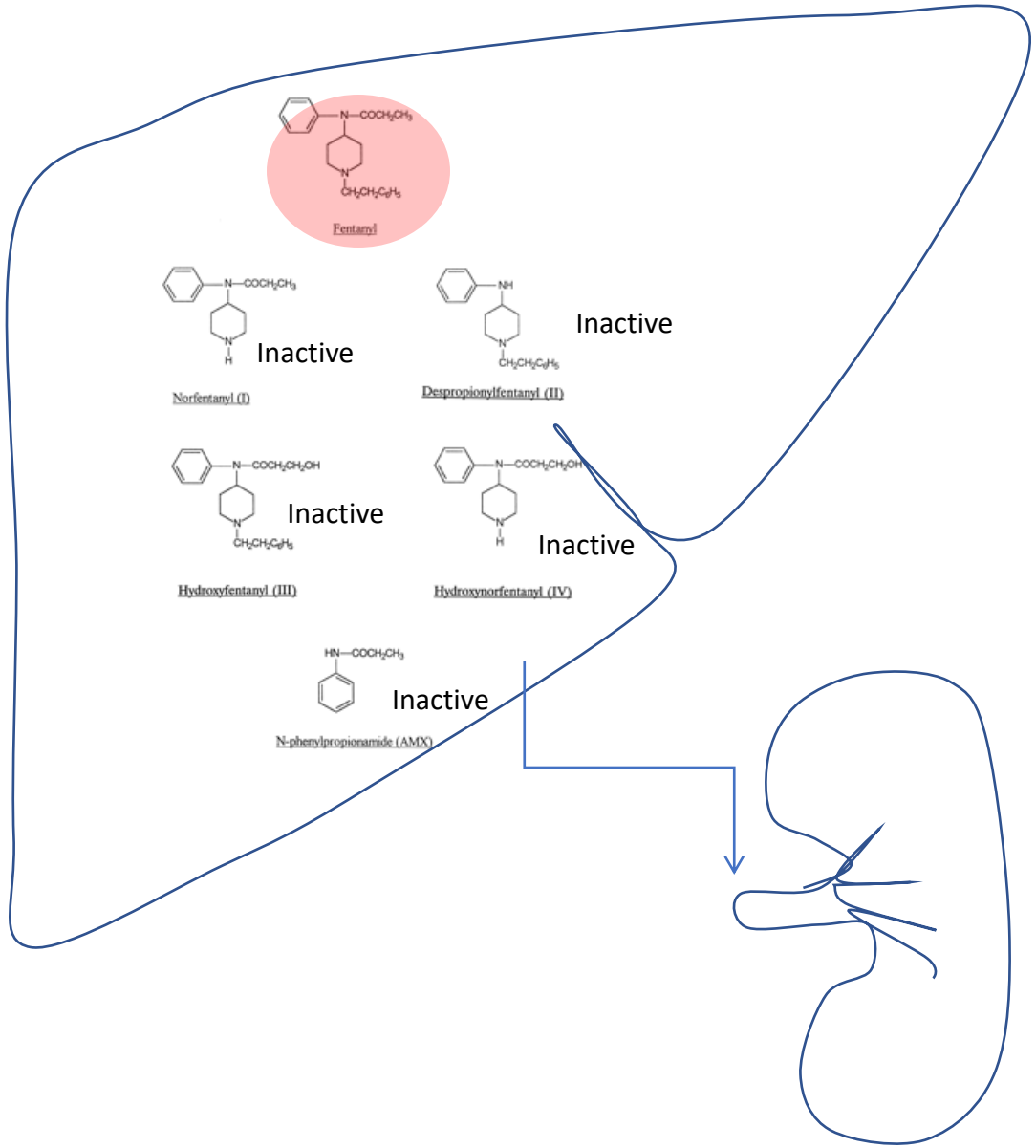
Methadone

- Methadone and its metabolites are excreted in the uren (20-50%) and feces (10-45% as Pyrrolidine metabolites)
- **No reports of adverse effects related to methadone have been reported in patients with CKD** (Johnson. Opioid Safety in Patients with Renal or Hepatic Dysfunction, 2007)



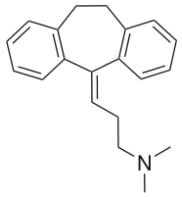
Fentanyl

- Metabolized to norfentanyl (99%) and other inactive metabolites
- **Renal clearance is reduced in moderate to severe uremia** (BUN>60mg/dL), causing post operative respiratory depression

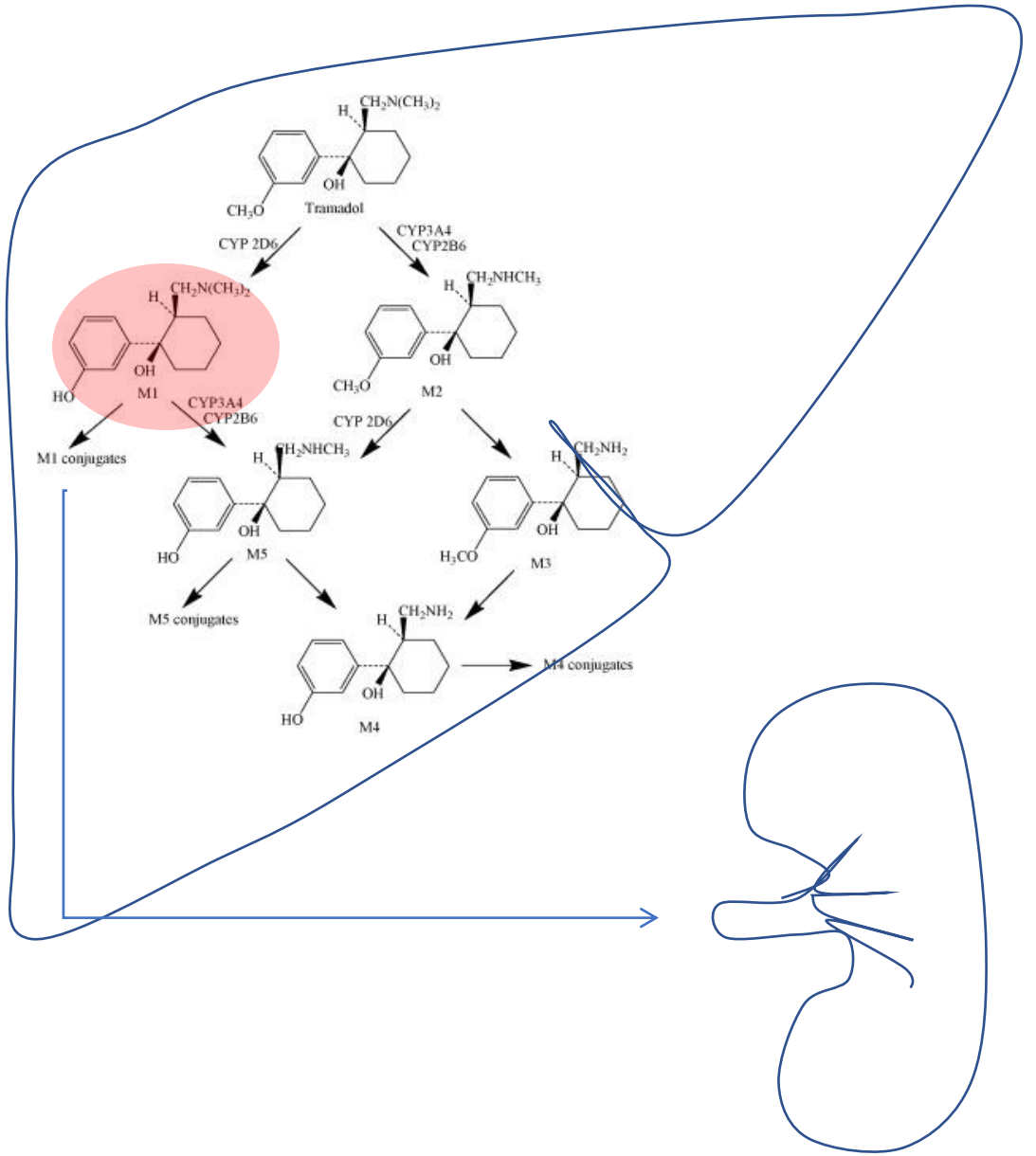


Tramadol

- M1 is only metabolically active metabolite
- **M1 is 6x more potent analgesic than Tramadol and has 200X mu binding affinity (in animal models)**
- **Has Tricyclic Antidepressant Properties**
- 30% renally excreted as unchanged drug
- 60% renally excreted, mostly M1→M4 metabolites
- Caution must be used in renal dosing due to accumulation of unchanged drug and M1, causing symptoms of opiate and/or SSRI toxicity

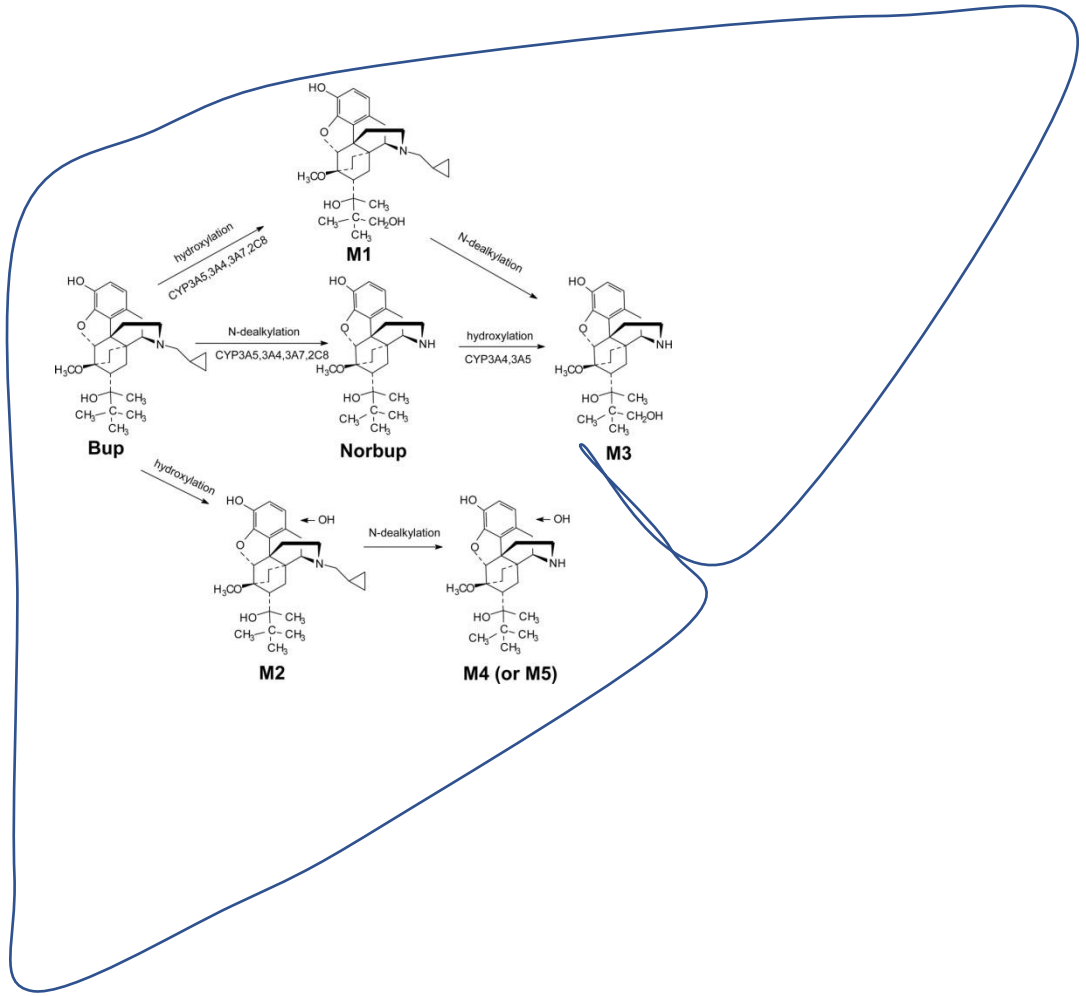


Amitriptyline



Buprenorphine

- **Pharmacokinetics not altered in CKD**



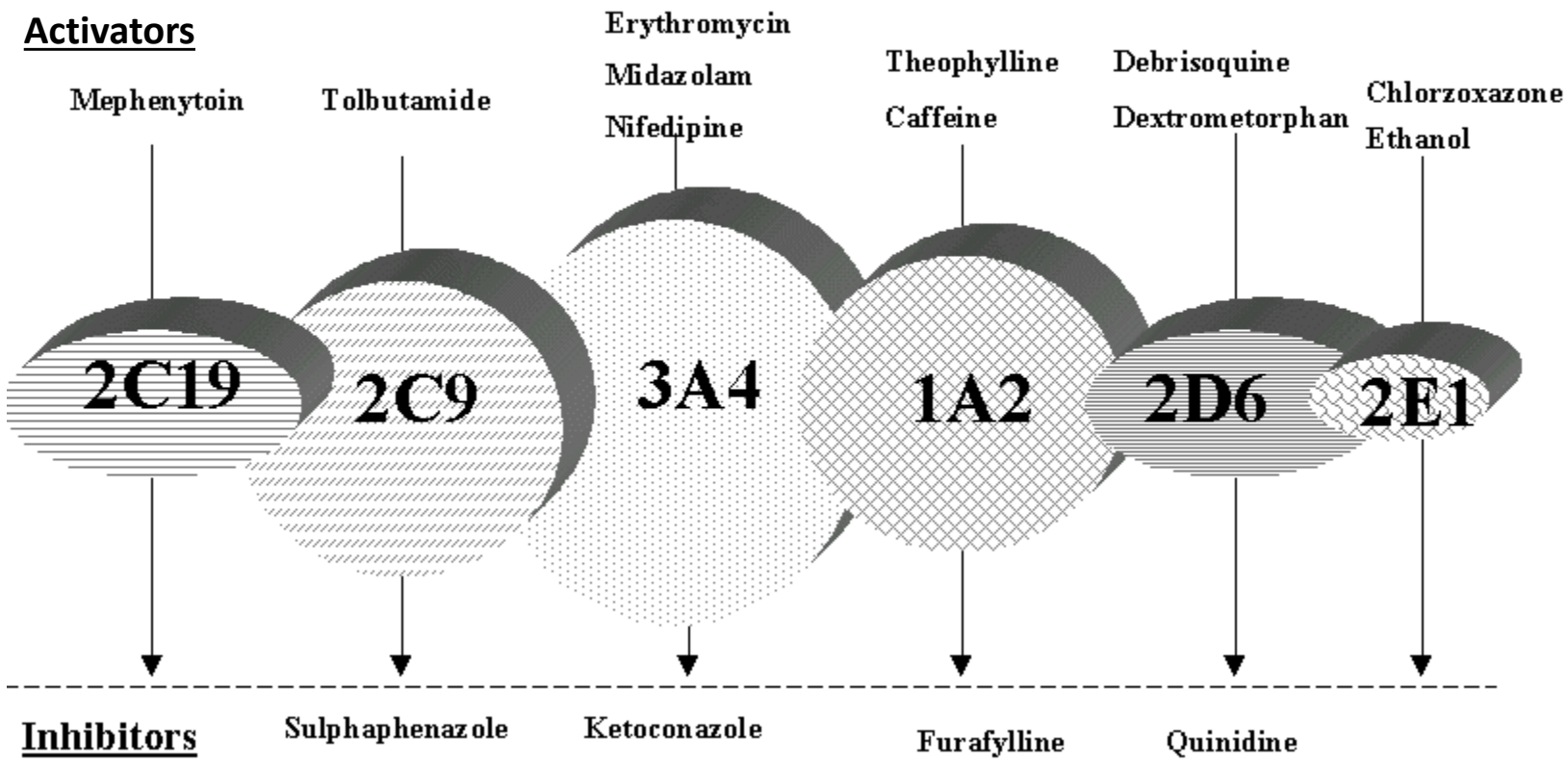
Metabolic Pathways of Opioids

Table 1. Metabolic Pathways of Common Opioids[12,83]

Opioid	Phase I Metabolism	Phase II Metabolism
Codeine	CYP2D6 CYP3A	UGT2B7
Hydrocodone	CYP2D6 CYP3A	UGT1A3 UGT2B7 Dihydromorphone ketone reductase
Oxycodone	CYP3A CYP2D6	UGT2B7
Methadone	CYP3A	
	CYP2B6	
	CYP2D6	
	CYP2C9[a]	
	CYP2C19[a]	
Tramadol	CYP3A	
	CYP2D6	
Fentanyl	CYP3A	
Morphine	CYP3A	UGT2B7
Hydromorphone		UGT1A3 UGT2B7 Dihydromorphone ketone reductase
Oxymorphone		UGT2B7

[a]Minor pathways/clinical significance unknown.
Adapted from Smith HS. *Mayo Clin Proc*. 2009;84(7):613-624 and Fredheim OM, Moksnes K, Borchgrevink PC, Kaasa S, Dale O. *Acta Anaesthesiol Scand*. 2008;52(7):879-889.

CYP 450 Enzymes



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