Opioid and Other Medications: How Do They Interact

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Learning Objectives

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1. Explain why prescriber education is important.
2. Overview of current addiction pharmacotherapy.
2. Review of current drug-drug interactions between opioids and other medications.
3. Review possible explanations for increases in drug-drug interactions.
4. Review physiological basis for adverse drug interactions .
5. Strategies for reducing risk.
6. List general drug information for Opioid Analgesic Products.

Learning Objectives

Identify	List	Identify	List
Identify the primary medications used to manage substance withdrawal and describe when they should be use.	List the drugs currently FDA-approved for the treatment of substance use disorders and provide a clinical illustration of appropriate use in primary care.	Identify a patient's stage of disease and whether and when to use pharmacotherapy including key indications and contraindications.	List major drug to drug interactions associated with opioid pharmacotherapy.

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New Behavioral Medications App

- **BHMEDS-R3 App**
- **Collaborating TTC: Mid-America ATTC**
- **Publication Date: November 5, 2019**
- **The BHMEDS-R3 app is designed as a quick reference for non-prescriber behavioral health professionals and consumers who need general knowledge about medications prescribed for behavioral health conditions. The language has been modified to increase readability for a larger audience and, in keeping with the goal of continuously updating the app content, new medications are added after FDA approval. Download the FREE app from the Google Play or iTunes store.**
- **Use the BHMEDS-R3 app for the following:**
- **Browse through different types of behavioral health medications**
- **Click a medication category icon to learn more details, including brand and generic names**
- **Use drop-down navigation menus to learn more about medications' purpose, dose and frequency, side effects, emergency conditions, misuse potential, and cautions.**
- **Access provider tools and other free medication resources**

Substance Use Disorders Pharmacotherapy

Pathophysiology of Drug-Drug Interactions

Pharmacokinetic:

what you do to the drug (or not)-**Body To Drug**

Pharmacodynamic (what the drug or drugs do to you)-

Drug To Body

Outline/Roadmap

- General considerations for SUD pharmacotherapy
- Alcohol
  - Acute withdrawal
  - Relapse prevention (ongoing pharmacotherapy)
- Opiates
  - Acute withdrawal
  - Relapse prevention
- Co-Occurring mental illness and psych medications
- (Nicotine will not be covered in this module but may serve as a useful example when considering medications to reduce craving or facilitate abstinence with other substances.)

When to Consider Pharmacotherapy

- **Assess Pt For:**
- **Severity of Concomitant Medical Illness: Patient's ability to tolerate medication?**
- **Pregnancy: opioid therapy should be offered to pregnant opioid/heroin addicts; medications that can be associated with adverse physical effects should be avoided (e.g.: disulfiram (Antabuse)**
- **Phase of Recovery: Medications for medical withdrawal or medication to assist with maintenance of abstinence following withdrawal**
-

Phases of Substance Use that are Targets for Pharmacotherapy

- Intoxication/overdose
- Withdrawal/detoxification
- Abstinence initiation/use reduction
- Relapse prevention
- Sequelae (psychosis, agitation, etc.)

Some Pharmacological Treatment Strategies for SUDs

- Agonist (replacement/substitution)
- Antagonist (blockade)
- Aversive (negative reinforcement)
- Correction of underlying/associated disorders (such as depression, etc.)

Substances for which Pharmacotherapy is Available

- Opioids
- Alcohol
- Benzodiazepines
- Tobacco (nicotine dependence)

Substances for which Pharmacotherapy is Not Available

- Cocaine
- Methamphetamine
- Hallucinogens
- Cannabis
- Solvents/Inhalants

Alcohol Use Disorder Pharmacotherapy

- Two Phases of Alcohol Use Disorder:
- 1. Acute Alcohol Withdrawal
- 2. Relapse Prevention: Maintenance Medications To Prevent Relapse To Alcohol Use (FDA approved)
    - Disulfiram
    - Naltrexone (oral and injectable)
    - Acamprosate
    - Note: **monitor any patient being treated for a SUD for emergence of depression/anxiety/ suicidality as this can occur in the course of treatment**
-

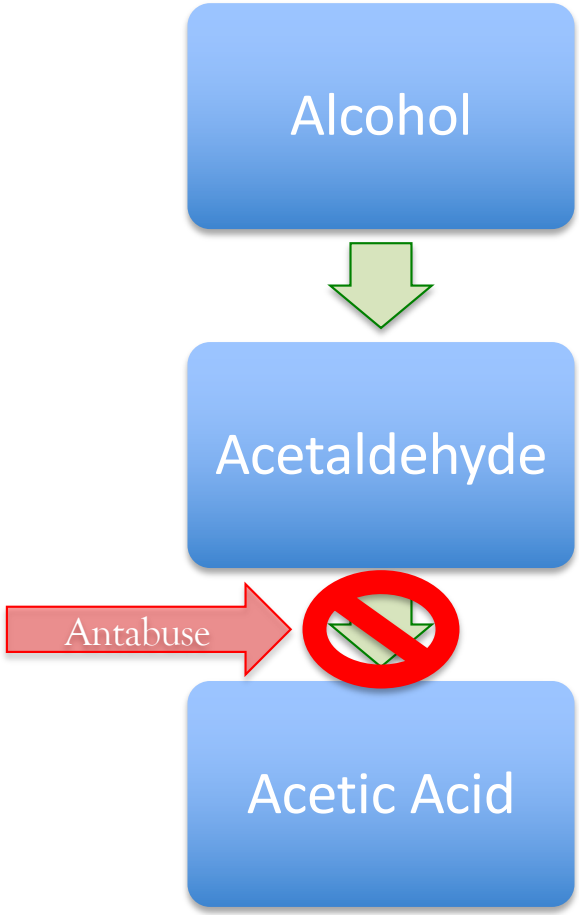
Alcohol Relapse Prevention Meds: Disulfiram (Antabuse)

- How it Works: Blocks alcohol metabolism leading to increase in blood acetaldehyde levels; aims to motivate individual not to drink because they know they will become ill if they do (Goodman and Gilman, 2001)
- Antabuse reaction: flushing, weakness, nausea, tachycardia, hypotension
  - Treatment of alcohol/disulfiram reaction is supportive (fluids, oxygen)
- Side Effects:
  - Common: metallic taste, sulfur-like odor
  - Rare: hepatotoxicity, neuropathy, psychosis
- Contraindications: cardiac disease, esophageal varices, pregnancy, impulsivity, psychotic disorders, severe cardiovascular, respiratory, or renal disease, severe hepatic dysfunction: transaminases > 3x upper level of nl
- Pt should avoid alcohol containing foods
- Clinical Dose: 250 mg daily (range: 125-500 mg/d)
- Some question whether patients adhere to this drug, but studies have shown positive benefits in terms of alcohol use disorder outcomes if the patient adheres; it is also a good idea to have the patient attend substance abuse treatment where, at least in the beginning of treatment, disulfiram is administered by staff/family (Fuller et al. 1994; Farrell et al. 1995)

- *See Clinical Tools Fact Sheet for more information*

Antabuse (Disulfiram)

- Alcohol abuse ***deterrent***
- Prevents second step in alcohol metabolism
- When alcohol is consumed:
  - Causes buildup of acetaldehyde
    - Flushing, nausea, and palpitation will occur
  - If effects are ignored and drinking continues, resuts may be fatal!



Antabuse (Disulfiram)

- **Wait at least 12 hours after drinking alcohol before beginning Antabuse**
- **Avoid alcohol in sauces, foods, and medications**
  - **Read Labels**
- **Avoid paint fumes, paint thinner, and shellac (nail polish)**
- **Use caution with colognes, aftershave, and rubbing alcohol.**

Antabuse (Disulfiram)

Black Box Warning
Disulfiram should never be administered to a patient when he is in a state of alcohol intoxication, or without his full knowledge. The physician should instruct relatives accordingly.

Campral (Acamprosate)

- **Used in conjunction with a treatment program**
- **Helps restore chemical balance**
  - **Increases GABA activity**
  - **Decreases glutamate activity**
  - **End result = blocking pain and less cravings**

GABA GLUTAMATE =

~~PAIN and CRAVINGS~~

Campral (Acamprosate)

- Reduces SECONDARY withdrawal symptoms
  - Insomnia
  - Anxiety
  - Restlessness
  - Uncomfortable moods
- Proven to help patients with severe dependence to remain
- abstinent for several weeks to months

Campral (Acamprosate)

Will not reduce or eliminate PRIMARY alcohol withdrawal symptoms;

Minor side effects including nausea, diarrhea, and dizziness may be due to alcohol abstinence not the medication

Must report feeling of depression, anxiety, or any suicidal thoughts to your health care provider.

Pharmacotherapy of Alcohol Use Disorder: Naltrexone

Oral Naltrexone Hydrochloride(Revia)

- DOSE: 50 mg per day

Extended-Release Injectable Naltrexone (Vivitrol) (Garbutt et al, JAMA 2005)

- 1 injection per month

Naltrexone Pharmacology

Similar structure to naloxone (Narcan)

Potent inhibitor of Mu opioid receptor binding

- may explain reduction of relapse
  - because endogenous opioids involved in the reinforcing (pleasure) effects of alcohol
- May explain reduced craving for alcohol
  - because endogenous opioids may be involved in craving alcohol

from *Littleton & Zieglgansberger, (2003) Am J Addict 12[Suppl1]:S3-S11*

Naltrexone Safety, 1

Can cause hepatocellular injury in very high doses (eg 5-10 times higher than normal)

Contraindicated in acute hepatitis or liver failure

check liver function before, q1 month for 3 months, then q 3 months

Caution about ibuprofen (Motrin, Advil, etc) and other non-steroidal anti-inflammatory agents

- may have additive hepatic effects

VA/DoD CPG SUDs, www.oqp.med.va.gov/cpg/SUD/SUD_Vase.htm

Vivitrol/ ReVia (Naltrexone)

Black Box Warning
Hepatotoxicity: Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone does not appear to be hepatotoxic at the recommended doses. **Warn patients of the risk of hepatic injury and advise them to seek medical attention if they experience symptoms of acute hepatitis**. Discontinue use of naltrexone in the event of symptoms and/or signs of acute hepatitis.

Naltrexone Safety, 2

Other contraindications

- concomitant opioid analgesics (naltrexone will block analgesic effect)
- opioid dependence or withdrawal
- hypersensitivity to naltrexone
- Medical conditions requiring opioid analgesics
- pregnancy (Category C)

Main adverse effects:

- gastrointestinal upset
- abdominal pain
- nausea
- vomiting
- headache
- dizziness

Naltrexone for Alcohol Use Disorder

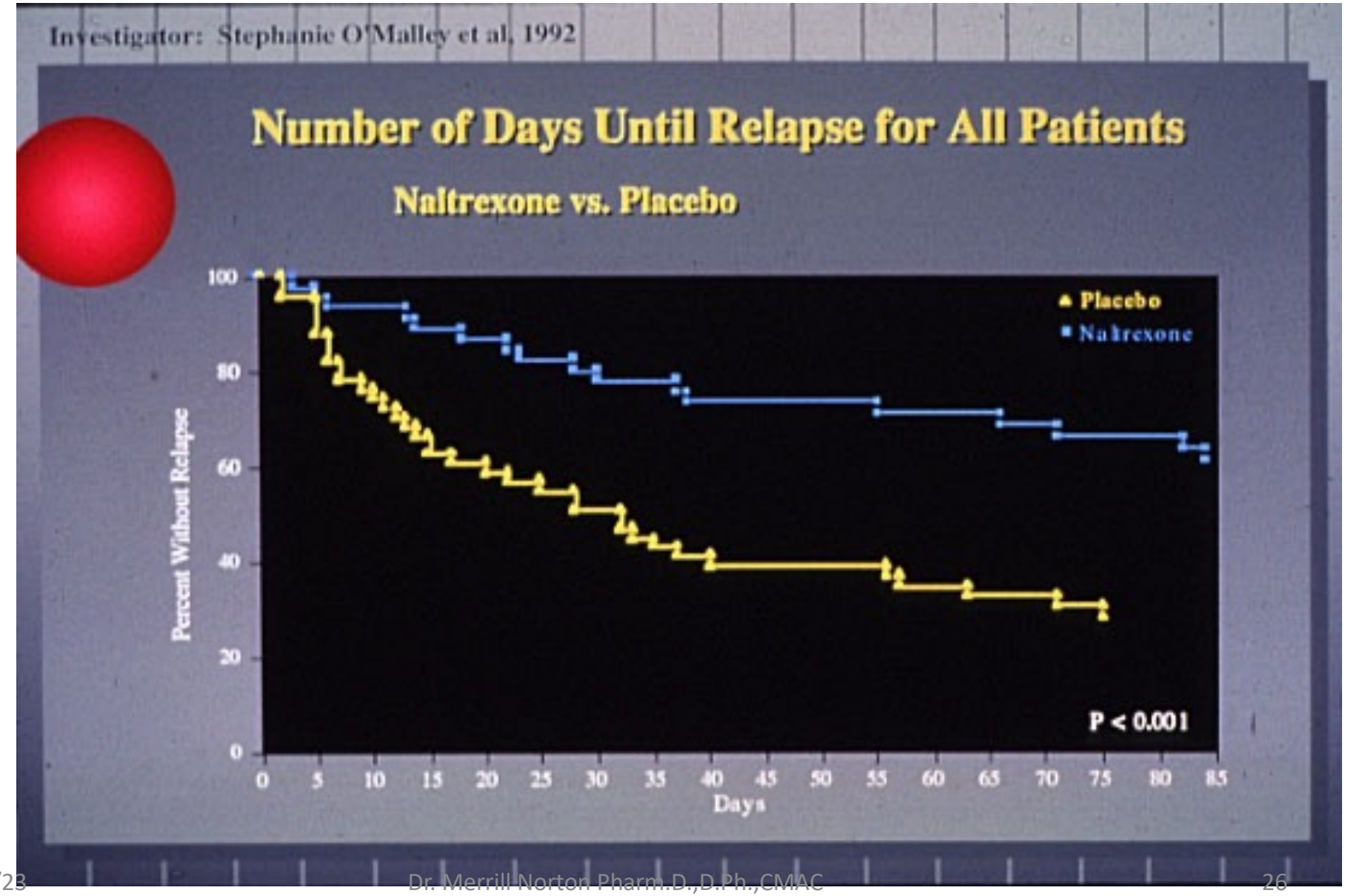
- Cochrane Review of NTX

  - ✦ decreased relapse to heavy drinking [RR = 0.64]
  - ✦ decreased return to any drinking [RR = 0.87]
  - ✦ NTX increased the time to first drink
  - ✦ NTX reduced craving
  - ✦ NTX was superior to acamprosate in reducing relapses, drinks and craving.

Srisurapanont & Jarusuraisin (2005) Cochrane Database Syst Rev.

2005 Jan 25;(1):CD001867

Naltrexone Delays the Onset of Relapse to Alcohol



What about Benzodiazepines for Alcohol Use Disorder?

Clinical Pearls: If your patient is alcoholic, try to avoid prescribing a BZD.

BZD produce cross-tolerance with alcohol

High risk of abuse of BZD

High risk of relapse to alcohol use

Combined use of alcohol and prescribed BZD can be very impairing and produce significant toxicity

If patient complains of anxiety:

- 1. consider use of serotonin reuptake inhibitors (this is first line treatment of anxiety disorders (not Benzos)),
- 2. refer to psychotherapeutic interventions (e.g.: cognitive-behavioral therapy),
- 3. consider relapse to alcohol

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But what if my patient can't sleep?

- Give patient sleep hygiene information (see Sleep Hygiene Handout attached to this module)
- Avoid so-called "non Benzo" sleep medications (e.g.: Ambien); these do have abuse liability, can produce intoxication syndromes, and may place patients with substance use disorders at higher risk for relapse
- Consider low dose trazodone (e.g. 25 mg) or qHS sedating antidepressant (especially if pt has co-morbid depression, e.g.:mirtazepine).
- APA, 2006

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Case Study

- A 42 year old man with a 14 year history of alcohol dependence relapsed to alcohol abuse 3 months ago. He currently reports drinking 3-5 drinks 4-5 times/wk, but states that he when he abstains for a day or two occasionally he does not experience alcohol withdrawal symptoms. However, his spouse is upset with his drinking and he now wants medication to help him to abstain. He tried naltrexone in the past, but says it 'didn't help much.' He takes no other medications and has no known allergies.
- What of the following would you recommend?
  - A. Liver function tests
  - B. Acamprosate 666 mg three times daily
  - C. Disulfiram 250 mg/d

Case Study: Answer

- A and C: This patient has a long and difficult history of struggling with alcoholism. He has failed naltrexone in the past and acamprosate is not likely to be helpful (the Combine Study showed it to be inferior to naltrexone). He has significant consequences of his drinking; is motivated to quit; therefore; if his liver functions indicate that he does not have significant impairment; a trial of disulfiram 250 mg daily might help.

Opioid Drug to Drug Interactions

Common Sites of DDIs

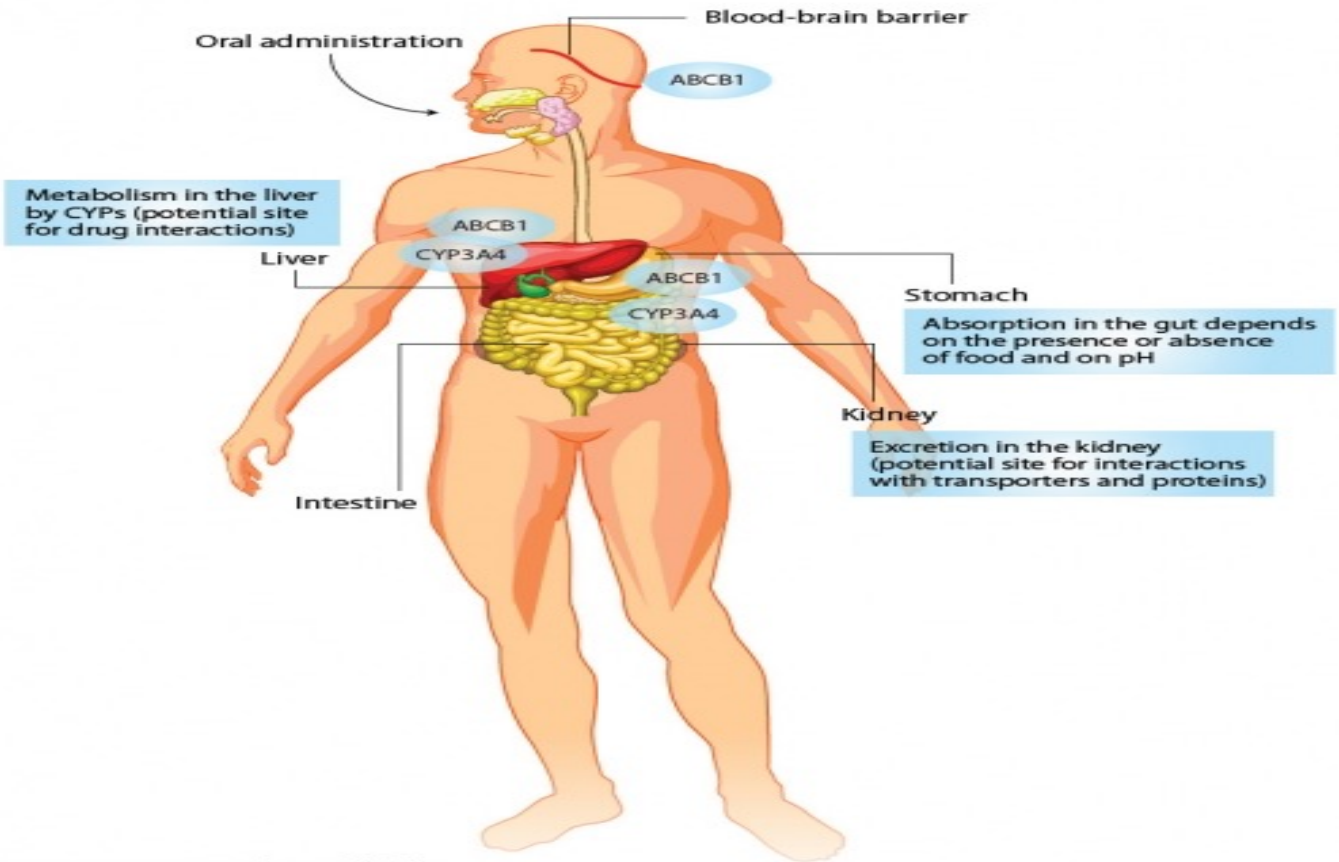


Figure 1. The most common sites of DDIs.
Adapted from Scripture CD, Figg WD. Drug interactions in cancer therapy. *Nat Rev Cancer.* 2006;6:546-558.
CYP, cytochrome P450

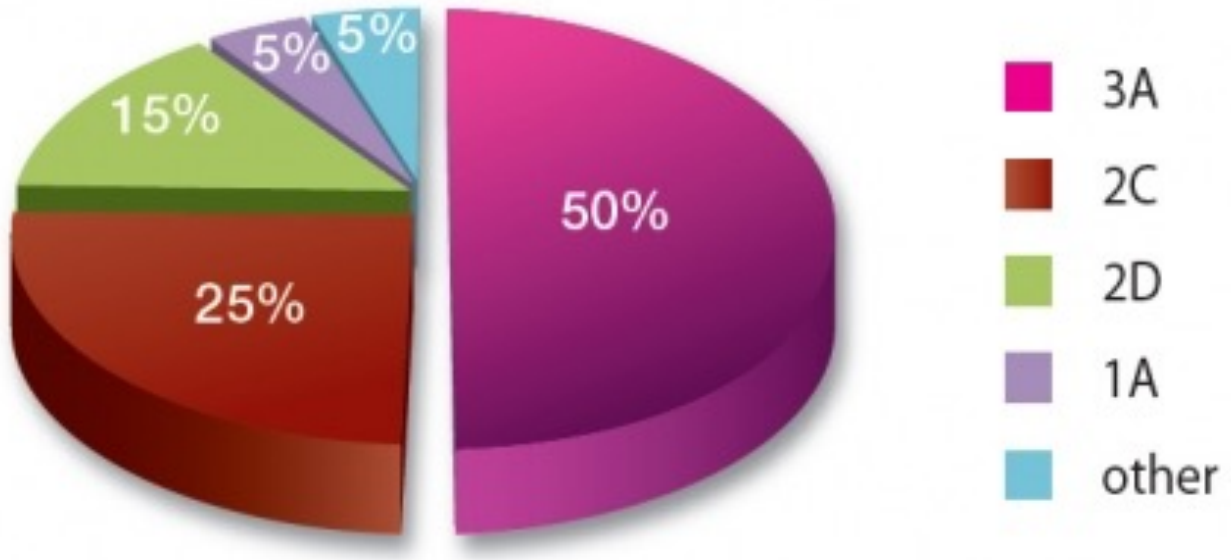


Figure 2. The approximate percentage of current drugs metabolized by each indicated CYP450 isozyme. Based on references 10,17,18.

Table 1. Some Common Inducers and Inhibitors of the CYP450 Isozymes Involved in the Metabolism of Opioid Drugs

CYP	Inducers
1A2	Barbiturates (ie, phenobarbital), carbamazepine, omeprazole, phenytoin, rifampin, tobacco smoke
2B6	Artemisinin, barbiturates, carbamazepine, efavirenz, nevirapine, phenytoin, rifampin
2C9	Barbiturates, phenytoin, rifampin, St. John's wort
2C19	Barbiturates, carbamazepine, lopinavir/ritonavir, phenytoin, rifampin, St. John's wort
2E1	Ethanol, isoniazid
3A4	Barbiturates, carbamazepine, corticosteroids (dexamethasone), efavirenz, modafinil, nevirapine, oxcarbazepine, phenytoin, rifabutin, rifampin, St. John's wort, troglitazone
CYP	**Inhibitors**
1A2	Cimetidine, fluoroquinolones, fluvoxamine, grapefruit juice, isoniazid
2B6	Clopidogrel, thiotepa, ticlopidine, voriconazole
2C9	Amiodarone, chloramphenicol, cimetidine, azole antifungals, isoniazid, metronidazole, SSRIs, probenecid, zafirlukast
2C19	Cimetidine, indomethacin, fluconazole, fluvoxamine, ketoconazole, lansoprazole, meprazole, modafinil, probenecid, SSRIs, topiramate
2D6	Amiodarone, chlorpromazine, cimetidine, cinacalcet, diphenhydramine, haloperidol, methadone, mibefradil, quinidine, fluoroquinolones, SSRIs, terbinafine, thioridazine
3A4	Amiodarone, azole antifungals, cimetidine, clarithromycin, diltiazem, erythromycin, fluoroquinolones, grapefruit juice, HIV protease inhibitors, quinine, SSRIs

CYP, cytochrome P450; HIV, human immunodeficiency virus; SSRIs, selective serotonin reuptake inhibitors
Based on references 8,9,21,22.

Table 2. Potential DDIs With Prescription Medications[a]

Opioid	US Brand Names[b]	CYP450 Isozyme	CYP Inducer or Inhibitor	Potential Result	Comment
Buprenorphine	Butrans Subutex Others	3A4 2C8 3A5 3A7 2C9 2C19 2C18	*Inducers* Barbiturates Carbamazepine Corticosteroids: dexamethasone Efavirenz Phenytoin Rifampin Troglitazone	Decreased blood level of buprenorphine, increased blood levels of metabolites	The oral bioavailability of buprenorphine is low, so other formulations are more commonly used. These bypass the first-pass effect and generate fewer metabolites. Thus, there is less opportunity for DDIs by these alternative routes. Transdermal ("patch") drug formulations bypass the first-pass effect and generate significantly fewer metabolites than do other administration routes on acute use. Metabolite levels can rise during long-term application. Buprenorphine is also formulated with naloxone (Suboxone). Naloxone undergoes only minor metabolism via CYP450 pathways.
			Inhibitors Amiodarone Azole antifungals Chloramphenicol Cimetidine Clarithromycin Cyclosporine Diazepam Diltiazem Erythromycin Fluoroquinolones HIV protease inhibitors Isoniazid Nefazodone Omeprazole Quinine SSRIs Tacrolimus Venlafaxine Verapamil Zafirlukast	Increased blood level of buprenorphine, decreased blood levels of metabolites	
Codeine	Numerous short-acting formulas	3A4 (to norcodeine) 2D6 (to morphine)	*Inducers* Barbiturates Carbamazepine Corticosteroids: dexamethasone Efavirenz Phenytoin Rifampin Troglitazone	Decreased blood level of codeine, increased blood levels of metabolites	Codeine is generally considered to be a prodrug of its active metabolite, morphine. Poor CYP-2D6 metabolizers have a poor analgesic response to codeine. Thus, CYP-2D6 inducers can increase the analgesic effect of codeine, and CYP-2D6 inhibitors can decrease its analgesic effect. Codeine is often combined with acetaminophen and aspirin.[c]
			Inhibitors Amiodarone Azole antifungals Bupropion Celecoxib Cimetidine Citalopram Clarithromycin Cyclosporine Diazepam Diltiazem Diphenhydramine Doxepin Duloxetine Erythromycin Escitalopram Fluoroquinolones Haloperidol HIV protease inhibitors Hydroxyzine Nefazodone Quinidine Quinine Sertraline SSRIs Tacrolimus Venlafaxine Verapamil	Increased blood level of codeine, decreased blood levels of metabolites	

Table 2. Potential DDIs With Prescription Medications[a] (Continued)

Opioid	US Brand Names[b]	CYP450 Isozyme	CYP Inducer or Inhibitor	Potential Result	Comment
Dihydrocodeine	Numerous	3A4 (to nordihydrocodeine) 2D6 (to dihydromorphine)	*Inducers* Barbiturates Carbamazepine Corticosteroids: dexamethasone Duloxetine Efavirenz Phenytoin Rifampin Troglitazone	Decreased blood level of dihydrocodeine, increased blood levels of metabolites	Often combined with aspirin, acetaminophen, and caffeine[c]
			Inhibitors Amiodarone Azole antifungals Bupropion Celecoxib Cimetidine Citalopram Clarithromycin Cyclosporine Diazepam Diltiazem Diphenhydramine Doxepin Erythromycin Escitalopram Fluoroquinolones Haloperidol HIV protease inhibitors Hydroxyzine Nefazodone Quinidine Quinine Sertraline SSRIs Tacrolimus Venlafaxine Verapamil	Increased blood level of dihydrocodeine, decreased blood levels of metabolites	
Fentanyl	Abstral Actiq Duragesic Fentora Lazanda Onsolis Subsys Others	3A4 (*N*-dealkylation)	*Inducers* Barbiturates Carbamazepine Corticosteroids: dexamethasone Efavirenz Phenytoin Rifampin Troglitazone	Decreased blood level of fentanyl, increased blood levels of metabolites	Transdermal ("patch") drug formulations bypass the first-pass effect and generate significantly fewer metabolites than do other administration routes on acute use. There is less opportunity for DDIs by these alternative routes. Metabolite levels can rise (accumulate) during long-term application.
			Inhibitors Amiodarone Azole antifungals Cimetidine Clarithromycin Cyclosporine Diazepam Diltiazem Erythromycin Fluoroquinolones HIV protease inhibitors Hydroxyzine Nefazodone Quinine SSRIs Tacrolimus Venlafaxine Verapamil	Increased blood level of fentanyl, decreased blood levels of metabolites	

Table 4. Commonly Encountered Prescription and Over-the-Counter Medications

Prescription Medications

- Beta blockers (ie, carvedilol, metoprolol, propranolol)—bradycardia[9]
- Glucocorticosteroids (prednisone)—reduction in potency[25]
- Antivirals (ie, clarithromycin, erythromycin, itraconazole, ketoconazole)—effects on efficacy[19]
- Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins: ie, atorvastatin, lovastatin, simvastatin)—muscle toxicity[25]
- Anxiolytics (ie, bupropion, diazepam, fluoxetine, paroxetine)—psychological performance[26]

Over-the-Counter Medications

- CYP450 enzymes metabolize some OTC medications[9]
  - Acetaminophen (Tylenol)
  - Ibuprofen (Advil, Motrin, Nuprin)
  - Loratadine (Claritin, Alavert)
  - Naproxen (Aleve, Naprosyn)
  - Omeprazole (Prilosec)
- CYP450 enzymes are inhibited by others[9]
  - Cimetidine (Tagamet)
  - Diphenhydramine (Benadryl)

Herbals

- *Ginkgo biloba* (ginkgo; family: Ginkgoaceae)—Certain components of *G. biloba* (such as amentoflavone) are potent in vitro inhibitors of human CYP-2C9[27,28]
- *Cimicifuga racemosa* (family: Ranunculaceae), commonly known as black cohosh—Black coshosh has been identified as a CYP-3A4 inhibitor[27,29]
- Frankincense (family: Burseraceae)—The oleo gum-resin obtained from trees of the genus Boswellia, frankincense has potential inhibitory activity on CYP-1A2, CYP-2C8, CYP-2C9, CYP-2C19, CYP-2D6, and CYP-3A4[27,30]
- *Gardenia jasminoides* (family: Rubiaceae)—The Merr fruit, which is well known as Cape Jasmine, inhibits CYP-3A[27,31]
- Chamomile (*Matricaria recutita*)—Chamomile demonstrated the inhibition of CYP-1A2, CYP-2C9, CYP-2D6, and CYP-3A4, with CYP-1A2 being the most sensitive of these enzymes[27,32]
- *Echinacea purpurea*. The commercial extract induced mild inhibition isoforms 1A2, 2C19, 2D9, and 3A4—with CYP-3A4 being the most, and CYP-2D6 the least sensitive enzyme[27,33]

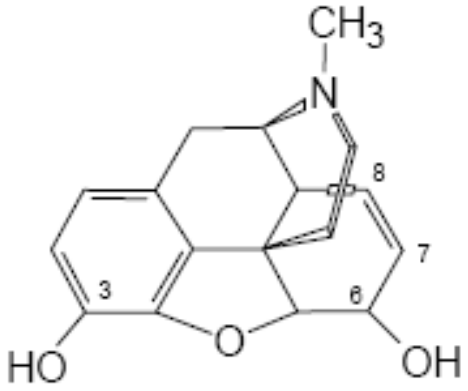
Pharmacotherapies for Opiate Use Disorder

Methadone

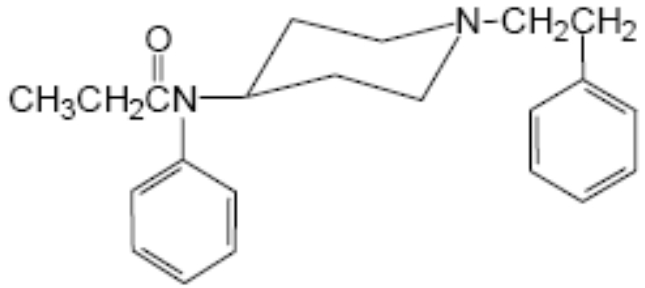
Buprenorphine

Naltrexone

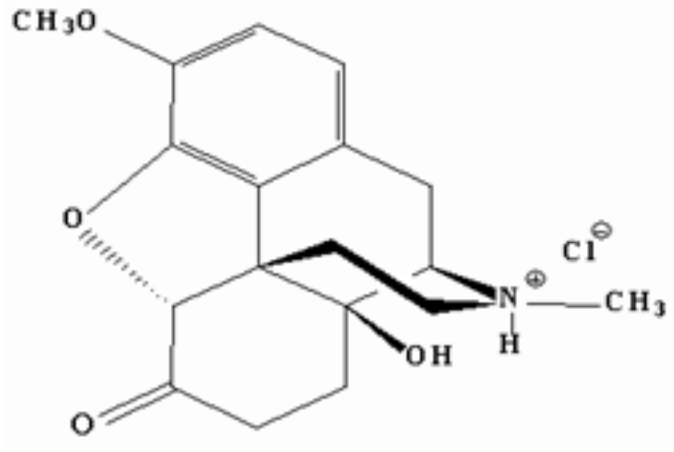
Naloxone (Rescue)



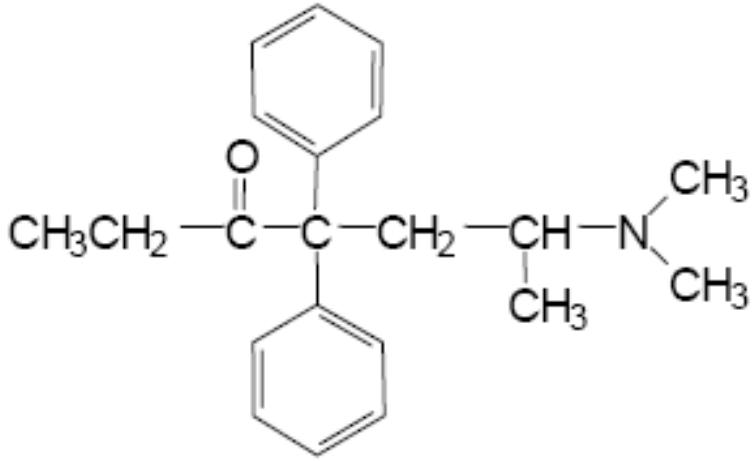
Morphine



Fentanyl



Oxycodone



Methadone

Genetic variability of morphine analgesia in Mouse Strains

Strain	Analgesia
BALB/c	90%
CD-1	76%
C57/bg^{J}	62%
HS	62%
C57/+	40%
Swiss Webster	40%
CXBK	0%

All animals received same mg/kg dose

Distinguishing Characteristics

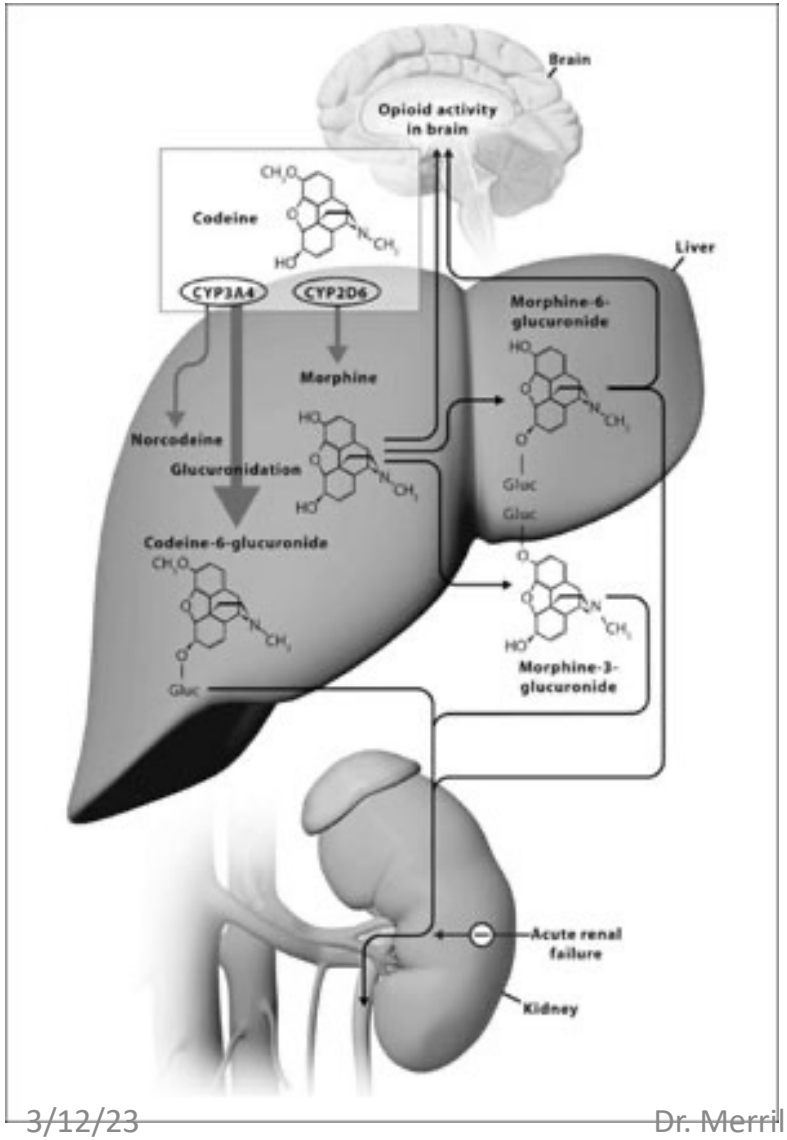
Pharmacokinetics

- Half life
- Metabolism

Pharmacodynamics

- Potency
- Most have one or two peculiarities

Codeine, morphine, hydromorphone metabolism



Glucuronidation
10% of codeine becomes morphine

Morphine and hydromorphone are both glucuronated to active metabolites.

Morphine and Hydromorphone

- Metabolized to 3-glucuronide metabolites
  - No analgesic properties
  - CSF doses often exceed doses of parent compound (rats)
  - Cause neuroexcitation
    - Smith MT Clin. Exper. Pharmacology Physiology 2000
- 6-glucuronide has analgesic properties
- Hydromorphone usually tolerated (low doses) as has shorter half-life than morphine?

Opioid Induced Neurotoxicity

- Definition
  - Neuroexcitability manifested by agitation, confusion, myoclonus, hallucinations and rarely seizures
- Predisposing Factors:
  - High opioid doses
  - Prolonged opioid use
  - Recent rapid dose escalation
  - Dehydration
  - Renal failure
  - Advanced age
  - Other psychoactive drugs
  - *Daeninck PJ, Bruera E. Acta Anaesthesiol Scand. 1999

Management of OIN

- Rehydration
- Treat concurrent causes of delirium e.g. UTI, pneumonia
- Reduce dose if pain controlled
- Switch to a different opioid

Fentanyl

- Targets mu and delta receptors
- 80-100X potency of morphine
- Rapid onset and very short half-life – needs to be delivered as parenteral infusion or transdermal patch for constant analgesia
- No active metabolites
- Highly lipophilic – useful in renal dialysis

Notes about the Fentanyl patch

- Takes 12 hours for onset of analgesia
- Need adequate subcutaneous tissue for absorption
- Takes 24 hours to reach maximum effect
- Change patch every 72 hours
- Dosage change after six days on patch

- Suitable for stable pain only

Sufentanil

- 10 fold more potent than fentanyl
- Lipophilic so can be absorbed through the buccal/sublingual mucosa
- Onset is 5-10 minutes, lasts 30 minutes
- Excellent for incident pain

Methadone

Supplied as a racemic mixture

- L methadone is mu agonist
- D methadone is NMDA receptor antagonist

May have greater efficacy in neuropathic pain

Half life variable but average is 24 hours – needs slow titration

Highly lipophilic – good in renal dialysis

Tramadol

- Weak opioid – mu receptor agonist
- Also inhibits reuptake of serotonin and noradrenalin
- Requires metabolism to become analgesic
- Maximal dose 400-600 mg day
- Useful for moderate pain

Buprenorphine

- Partial agonist of mu receptor
- Requires metabolism to become analgesic
- Slow onset, highly bound to receptor
- Ceiling effect – consider as a weak opioid
- Comes in patch that lasts 7 days
- Useful for moderate pain

Opioid Use Disorder Therapy: Agonist Treatment

- What is agonist therapy?
- Use of a ***long acting*** medication in the same class as the abused drug (once daily dosing)
  - Prevention of Withdrawal Syndrome
  - Induction of Tolerance
- What agonist therapy is not:
  - Substitution of "one addiction for another"
- Who is appropriate for methadone therapy?
  - ≥ 18 years (exceptions for 16-17 y.o. with parental consent and special methadone treatment programs)
  - Greater than 1 year of opioid dependence
  - Medical compromise
  - Infectious disease
  - Pregnancy (CSAT 2005)

Opioid Use Disorder Maintenance Therapy

- **Determine Opioid Use Disorder**
  - History (including previous records)
  - Signs of dependence (withdrawal symptoms, tracks)
  - Urine toxicology
  - ECG: determine if pre-existing prolonged QT interval, ECG after 30 days to compare to baseline; methadone prolongs QT in approx. 2%
  - Naloxone challenge can be given if unsure of opioid use disorder
  - Clinical Opiate Withdrawal Scale can be used to determine extent of opiate withdrawal symptoms

Opioid Use Disorder Maintenance Therapy

- **Methadone**
  - Can interact with many commonly used medications
    - Decreased methadone concentrations:
      - Pentazocine
      - Phenytoin
      - Carbamazepine
      - Rifampin
      - Efavirenz
      - Nevirapine
      - Lopinavir (Kaletra)
        - Opiate withdrawal syndrome
  - Increased methadone concentrations:
    - Ciprofloxacin
    - Fluvoxamine
    - Discontinuation of inducing drug
      - Cognitive impairment
      - Respiratory depression
      - QTc prolongation; Torsade de Pointes

        - McCance-Katz et al. 2009

Opioid Use Disorder Maintenance Therapy

- **Methadone**
  - Benefits:
    - Lifestyle stabilization
    - Improved health and nutritional status
    - Decrease in criminal behavior
    - Employment
    - Decrease in injection drug use/shared needles

- CSAT, 2005

Opioid Use Disorder Maintenance Therapy

- **Methadone** (must be administered through a registered opioid treatment program)
  - Characteristics
    - Long acting mu agonist
    - Duration of action: 24-36 h
    - Dose: important issue and philosophical issue for many programs
    - 30-40 mg will block withdrawal, but not craving
    - Illicit opiate use decreases with increasing methadone dose
    - 80-100 mg is more effective at reducing opioid use than lower doses (e.g.: 40-50 mg/d)
    - Strain et al. 1999

Opioid Use Disorder Therapy: Antagonist Treatment

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

- **Naltrexone**
- Why antagonist therapy?
  - Block effects of a dose of opiate (Walsh et al. 1996)
  - Prevent impulsive use of drug
  - Relapse rates high (90%) following detoxification with no medication treatment
  - Dose (oral): 50 mg daily, 100 mg every 2 days, 150 mg every third day
  - Blocks agonist effects
  - Side effects: hepatotoxicity, monitor liver function tests every 3 months
  - Biggest issue is lack of compliance; but those who “test” naltrexone by taking a dose of opioid and experiencing no effect do better with the medication (Cornish JW, et al. 1997)
  - Injectable naltrexone not currently approved for opioid dependence, but likely to also be effective

Who is a Candidate for Naltrexone?

- The patient is opioid free for 7-10 days
- The patient does not have severe or active liver or kidney problems (Typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal, and bilirubin normal)
- The patient is not allergic to naltrexone, and no other contraindications are present (rarely would someone be allergic to naltrexone, but opioid addicted individuals sometimes may report an allergy as this is not a preferred treatment or they may have started naltrexone before being completely withdrawn from opioids and experienced precipitated withdrawal—ask patient about the time frame of adverse events when trying to evaluate)

Mental Illness in SUDs

- Among those with an alcohol disorder, 37% had a comorbid mental disorder.
- Among those with non-alcohol drug disorders, more than half (53%) were found to have a mental disorder, with an odds ratio of 4.5

(Regier 1990 JAMA)

SUDS in Mental Illness

- Among those with a mental disorder, the odds ratio of an addictive disorder was 2.7, with a lifetime prevalence of about 29%
  - ◆including an overlapping 22% with an alcohol use disorder,
  - ◆and 15% with another drug disorder

(Regier 1990 JAMA)

Why Use Psychiatric Medications in Patients with SUD Comorbidity?

1. To treat psychiatric disorders

2. To attempt to treat substance use disorders

- directly or indirectly

Reluctance to Prescribe

- Lack of available prescribing providers
- Concerns about psychological issues: over-reliance on medications
- Concerns about “enabling”
- Concerns about medication safety and related issues

Concerns regarding the use of psychiatric medications in SUD

Abuse potential

Safety

- Side effects
- Overdose
- Interactions w. substance

Effectiveness

- Antianxiety agents
- Antidepressants
- ADHD medications
- Mood stabilizers
- Antipsychotics
- Sleep medications (sedative-hypnotics,etc.)

Abuse Liability

Are psychiatric medications abusable/addictive?

Two relevant questions:

- Are they rewarding?
- Do they cause physiological dependence?

A related question:

Are they sedating?

Abuse Potential of Psychiatric Medications

LITTLE/NONE	SOME	SIGNIFICANT
Antipsychotics*	**Tricyclic antidepressants**	**Benzodiazepines**
Mood stabilizers	**Anticholinergic antiparkinsonians**	**Barbiturates**
Most anticonvulsants		**Stimulants**
Non-tricylcic antidepressants		
buspirone		
* little or none (however, sedating atypical APs may be overused, e.g. quetiapine	?zolpidem ?zaleplon ?eszopiclone ?pregabalin ??modafinil	

Combining Drugs and Alcohol with Psychiatric Medications: Drug Interactions

Medications

Alcohol

Drugs

Alcohol & Atypical Antipsychotics: Oversedation

May be a risk with

- clozapine
- olanzapine
- quetiapine
- risperidone

Less likely to be a risk with

- ziprasidone

Unlikely to be a risk with

- aripiprazole

Alcohol and Antidepressants

additive impairment with sedating ADs,

- tricyclics
- mirtazapine (PDR)
- fluvoxamine (PDR)

no apparent additive impairment:

- SSRIs (PDR)
  - paroxetine, sertraline, citalopram
- venlafaxine (PDR)
- nefazodone
- Bupropion (caveat: may lower seizure threshold)

Alcohol:
Interactions with
Psych
Meds/Substances

Effects of alcohol depend on:

- Amount
- Rate of absorption
- Tolerance

Opioids, benzodiazepines:

- increased CNS depression

Cocaine: increased cardiac toxicity, rapid heart rate, high BP

Opioids: Interactions with Psych Meds/Substances

- Methadone:
  - Tricyclic antidepressants: raise methadone levels & vice versa
  - Fluvoxamine: raises methadone levels to dangerous/life-threatening levels; other SSRIs (fluoxetine, paroxetine) may also inhibit methadone and have been associated with toxicity
  - Carbamazepine: lowers methadone levels, as do (to a lesser degree) phenobarbital and phenytoin

Maxwell and McCance-Katz, Am J Addictions, 2009

Opioids: Interactions with Psych Meds/Psychoactive Substances

- All opioids:
  - benzodiazepines: increased CNS depression, respiratory depression, death
  - alcohol: increased CNS depression

Cocaine: Interactions with Psych Meds/Psychoactive Substances

Epinephrine (and probably other sympathomimetic drugs):

- cardiac arrhythmias

MAO inhibitors: hypertensive crisis

Alcohol: more toxicity, hypertension, tachycardia

Antipsychotics: increased potential for seizures, rigidity, hyperthermia

Amphetamines: Interactions with Psych Meds/Psychoactive Substances

MAO inhibitors: hypertensive crisis

Antipsychotics: increased potential for seizures, rigidity, hyperthermia

Potential for serotonin syndrome in combination with serotonin-increasing medications

Antidepressants in Co-occurring Depression and SUDs

Treatment of Depression in Patients With Alcohol or Other Drug Dependence (A Meta-analysis) Nunes (2004 JAMA, April 21,, vol 291, 15, p1887-1896

- 14 randomized, double-blind, placebo-controlled, meet diagnostic criteria for current unipolar depression and current substance dependence (N=848 patients)
- 8 studies (alcohol), 4 studies (methadone), 2 cocaine

Courtesy of John Tsuang, M.D.

Nunes (2004) - Results

- Diagnosis of depression after one week of abstinence was associated with greater antidepressant effect
- Antidepressant medication effective for treatment of depressive syndromes among patients with substance dependence
- Antidepressant medication can diminish quantity of substance use but not helpful in sustained abstinence
- Improvement in substance use correlated with improved depression regardless of medication response

Courtesy of John Tsuang, M.D.

Nunes (2004) - Conclusions

- If diagnosis of depression, then a period of abstinence is preferred but not required for antidepressant tx
- Current recommendations are that alcohol and drug abuse not to be a barrier to treatment of depression
- Antidepressant treatment may have some impact on alcohol and drug use (reduced amount vs. abstinence); but consider drug interactions in weighing risk/benefit

Courtesy of John Tsuang, M.D.

Case Study

- Ms. D is a 25 y.o. woman who receives treatment for asthma. Her usual medications are theophylline and an albuterol inhaler. She also has a 3 yr h/o cocaine abuse and says that her use has increased steadily over the past 6 months so that she now uses 3-4 times weekly, up to 1 gram each time (her urine drug screen is positive for cocaine metabolite). In the past year, she has began to experience paranoid thinking with her cocaine use. She reports at this visit that she continues to hear voices even when she is not using cocaine. She finds this disturbing and asks for help. What can be offered to this patient?

Case Study

- This patient appears to be cocaine dependent. She has been increasing her use of the drug and continues this even though you have told her that smoking cocaine can worsen her asthma and she is experiencing paranoia associated with cocaine abuse. She needs further evaluation and treatment, referral to a substance abuse treatment program such as an intensive outpatient program. Her report of continuing psychosis warrants a trial of antipsychotic medication (haloperidol or risperidone 0.5 mg at hs; increased to 0.5 mg twice daily if needed) for a few weeks; and ongoing evaluation of mental status. If psychosis continues with discontinuation of cocaine use; she should be referred to psychiatry for evaluation and ongoing treatment as she may have developed an independent psychotic disorder.

What About Cannabis and Opioids?

- **Three cannabinoids are being studied: CBD, THC, and CBN;**
- **The conventional opioids most commonly used for chronic pain management are morphine, oxycodone, codeine, methadone, tramadol, and fentanyl;**
- **CBD inhibits UGT2B7, and thus, a lower M6G to morphine ratio should be expected and less analgesic potency.**

- Marta Vázquez, Natalia Guevara, Cecilia Maldonado, Paulo Cáceres Guido, Paula Schaiquevich, "Potential Pharmacokinetic Drug-Drug Interactions between Cannabinoids and Drugs Used for Chronic Pain", *BioMed Research International*, vol. 2020, Article ID 3902740, 9 pages, 2020. https://doi.org/10.1155/2020/3902740

What About Cannabis and Opioids?

- **CBD, THC, and CBN inhibit CYP2D6 affecting oxymorphone formation and thus reducing analgesic effect**
- **The other problem is enhanced analgesic effect of CBD, THC, and CBN which can lead to overdose if not observed.**

- Marta Vázquez, Natalia Guevara, Cecilia Maldonado, Paulo Cáceres Guido, Paula Schaiquevich, "Potential Pharmacokinetic Drug-Drug Interactions between Cannabinoids and Drugs Used for Chronic Pain", *BioMed Research International*, vol. 2020, Article ID 3902740, 9 pages, 2020. https://doi.org/10.1155/2020/3902740

The Journal of the American Osteopathic Association
Established 1901

From: **Role of Opioid-Involved Drug Interactions in Chronic Pain Management**

J Am Osteopath Assoc. 2019;119(12):839-847. doi:10.7556/jaoa.2019.136

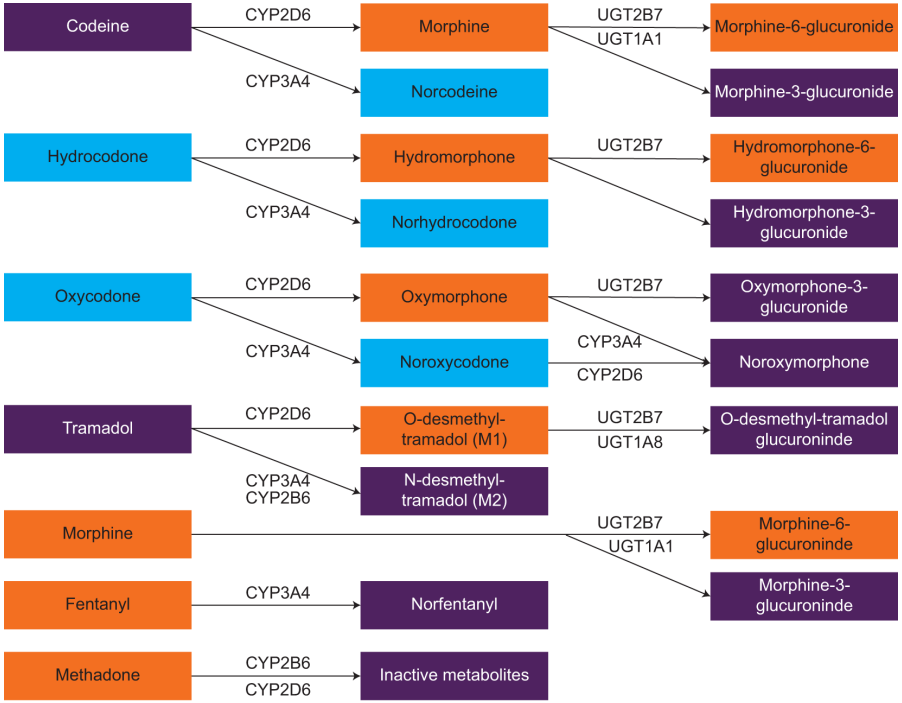


Figure Legend:

Metabolic pathways of commonly used opioids.[13,17,18,23-25] Drugs and metabolites in purple shading have no analgesic effects to relatively weak analgesic effects, blue shading indicates those having relatively moderate analgesic effects, and orange shading indicates those having relatively strong analgesic effects. Compiled from various sources. Some pathways and metabolites (eg, glucuronidation of codeine to codeine-6-glucuronide) have been purposefully omitted for brevity. Abbreviations: CYP, cytochrome P450 system; UGT, uridine-diphospho-glucuronosyltransferase.

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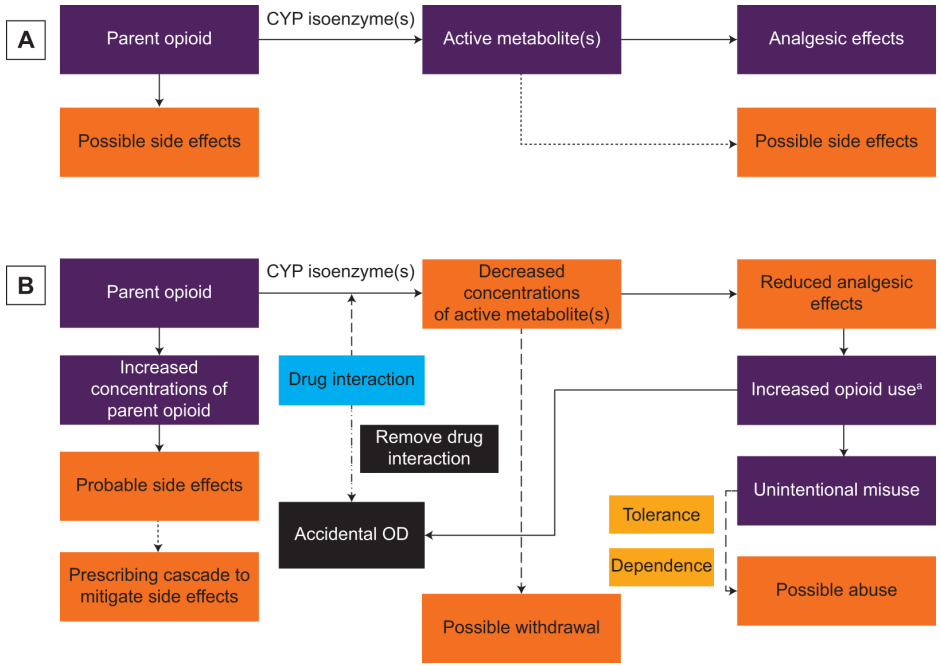

Figure Legend:

Consequences of opioid-involved drug interactions. (A) Expected responses in the absence of a drug interaction. (B) Predicted responses in the presence of a drug interaction. Abbreviations: CYP, cytochrome P450 system; OD, overdose. [a]Patient takes more opioid than prescribed and/or health care professional prescribes higher opioid doses to try and overcome the reduced analgesic effects.

Take Home Points

- Three medications have been FDA-approved for the maintenance treatment of alcoholism: disulfiram, naltrexone (oral daily or injectable once monthly), and acamprosate
- Three medications are FDA-approved for treatment of opioid addiction: naltrexone (an opioid antagonist best for highly motivated patients), methadone (must be given through a licensed narcotic treatment program), and buprenorphine/naloxone (available by prescription from qualified providers).
- Some meds are appropriate adjuncts in primary care and should be considered part of the “toolbox” for treating addictions.

Tools and Resources

- Disulfiram Fact Sheet http://www.healthyplace.com/other-info/psychiatric-medications/antabuse-disulfiram-patient-sheet/menu-id-72/
- Naltrexone Information Sheet http://familydoctor.org/online/famdocen/home/common/addictions/alcohol/130.html
- Acamprosate Information: http://kap.samhsa.gov/products/brochures/advisory/text/Acamprosate-Advisory.doc
- Clinical Opiate Withdrawal Scale (COWS)

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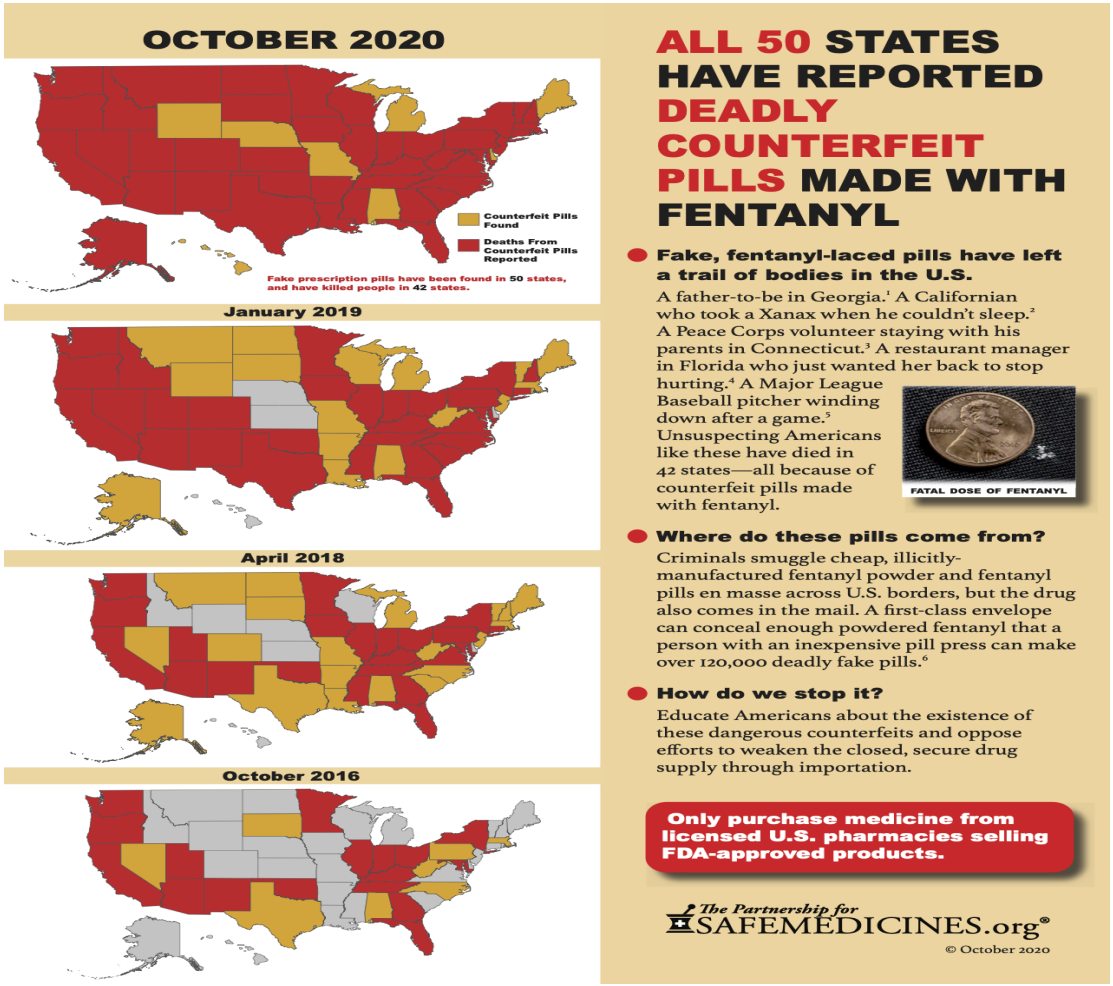
Counterfeit Drugs

Fentanyl in counterfeit pills in all 50 states



What Are Counterfeit Drugs?

- Counterfeit medicine is fake medicine and may be harmful to your health.
- However, incidence of counterfeit drugs in the U.S. is rare relative to the large number of prescription drugs used. FDA remains vigilant to protect the U.S. drug supply from counterfeits and other substandard drugs that often originate from outside our boarders.
- Since many counterfeits are made abroad and can arrive in the U.S. through the mail or are smuggled in, FDA works with U.S. Customs and Border Protection, and using a risk-based approach focuses on areas that present the most threat to our drug supply.

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Counterfeit Drugs = Fentanyl

- Counterfeit drugs are fake look alike medications
- They often originate from outside the US
- These drugs commonly contain fentanyl, which is highly potent and potentially deadly

← A lethal dose of fentanyl

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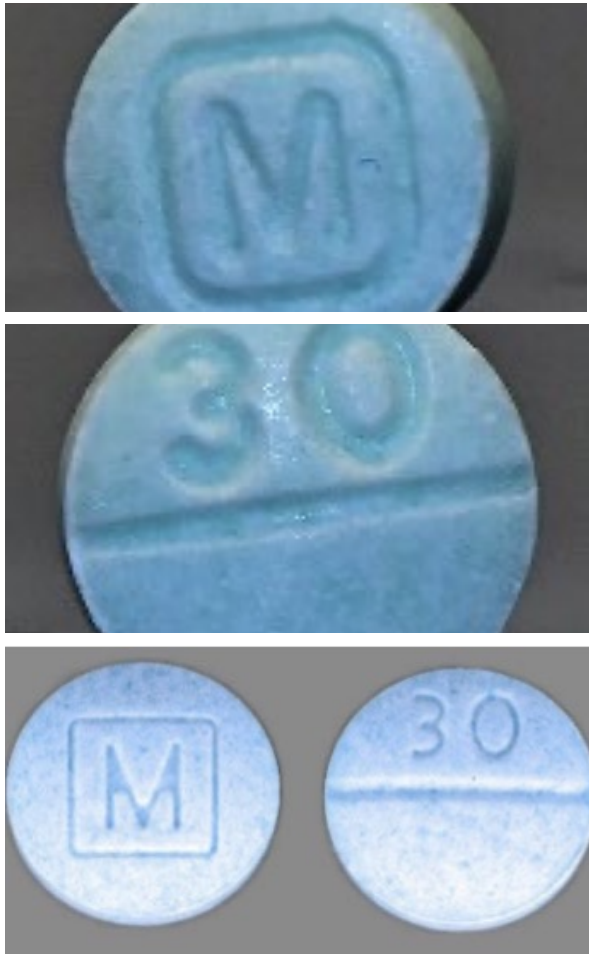


Counterfeit Drugs

- These drugs often lead to opioid overdose

Top: Authentic oxycodone 30mg

Bottom: Counterfeit oxycodone 30mg mixed with fentanyl

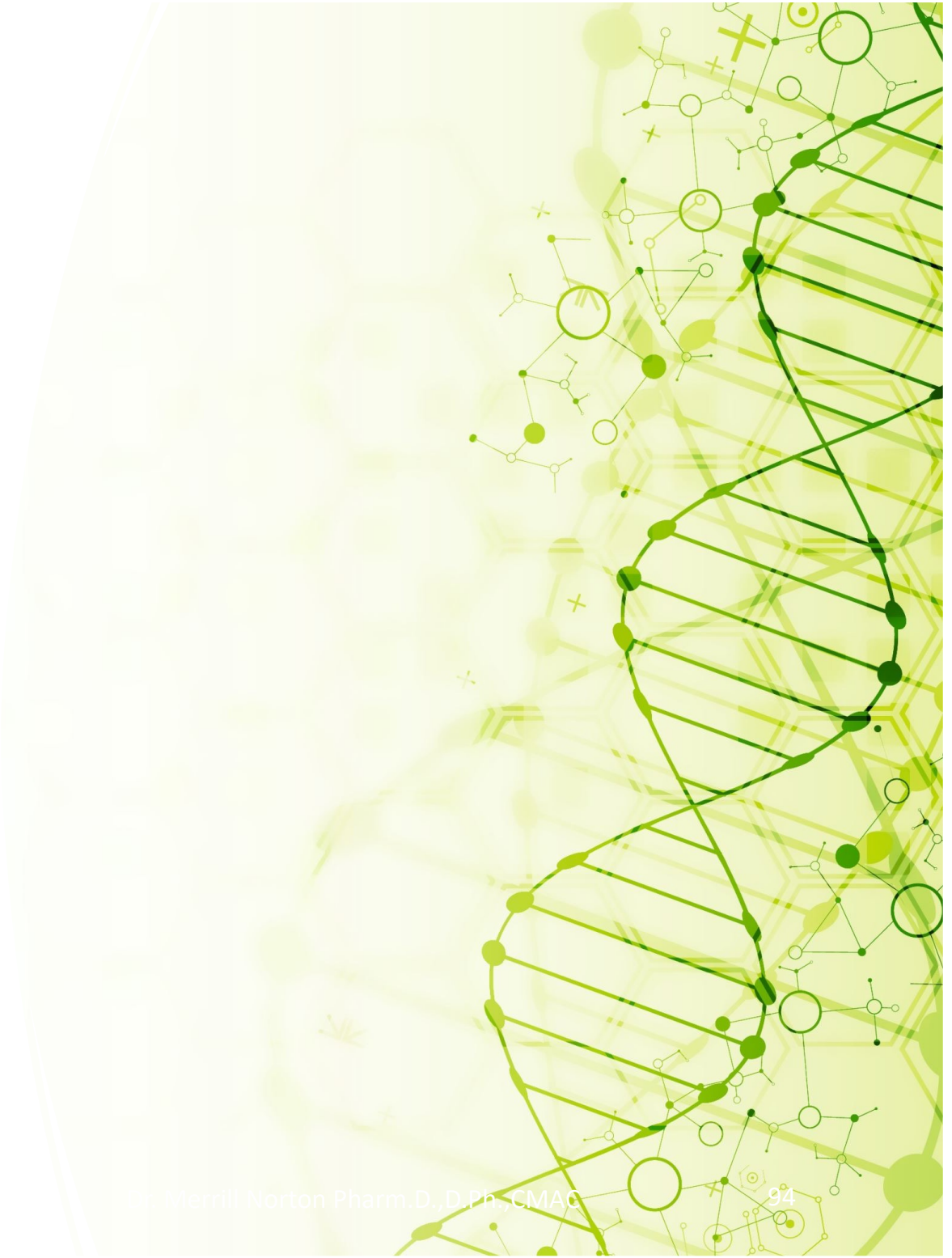
Counterfeit Opioid Medications

- *Authentic Adderall tablets (top) vs. counterfeit Adderall tablets containing methamphetamine (bottom).*

Counterfeit Opioid Medications

- *Authentic Xanax tablets (white) vs. counterfeit Xanax tablets containing fentanyl (yellow).*

Fentanyl and Carfentanil



Fentanyl Citrate/Fentanyl HCL
Schedule II

What Is Fentanyl?

- Fentanyl is 80-100 times stronger than morphine
- It is a potent prescription synthetic opioid that is used for cancer pain management
- Fentanyl is typically used as a transdermal patch
- Street names for Fentanyl include Apace, China Girl, and Dance Fever
- Fentanyl is often added to heroin for increased potency, leading to many overdose deaths

What Is Carfentanil ?

Carfentanil is a tranquilizing agent used for elephants and other large mammals

It is not meant for use in humans due to its dangerously high potency

Carfentanil is 10,000 times more potent than morphine and 100 times more potent than fentanyl

Fatal overdoses have occurred from counterfeit pills that contain carfentanil

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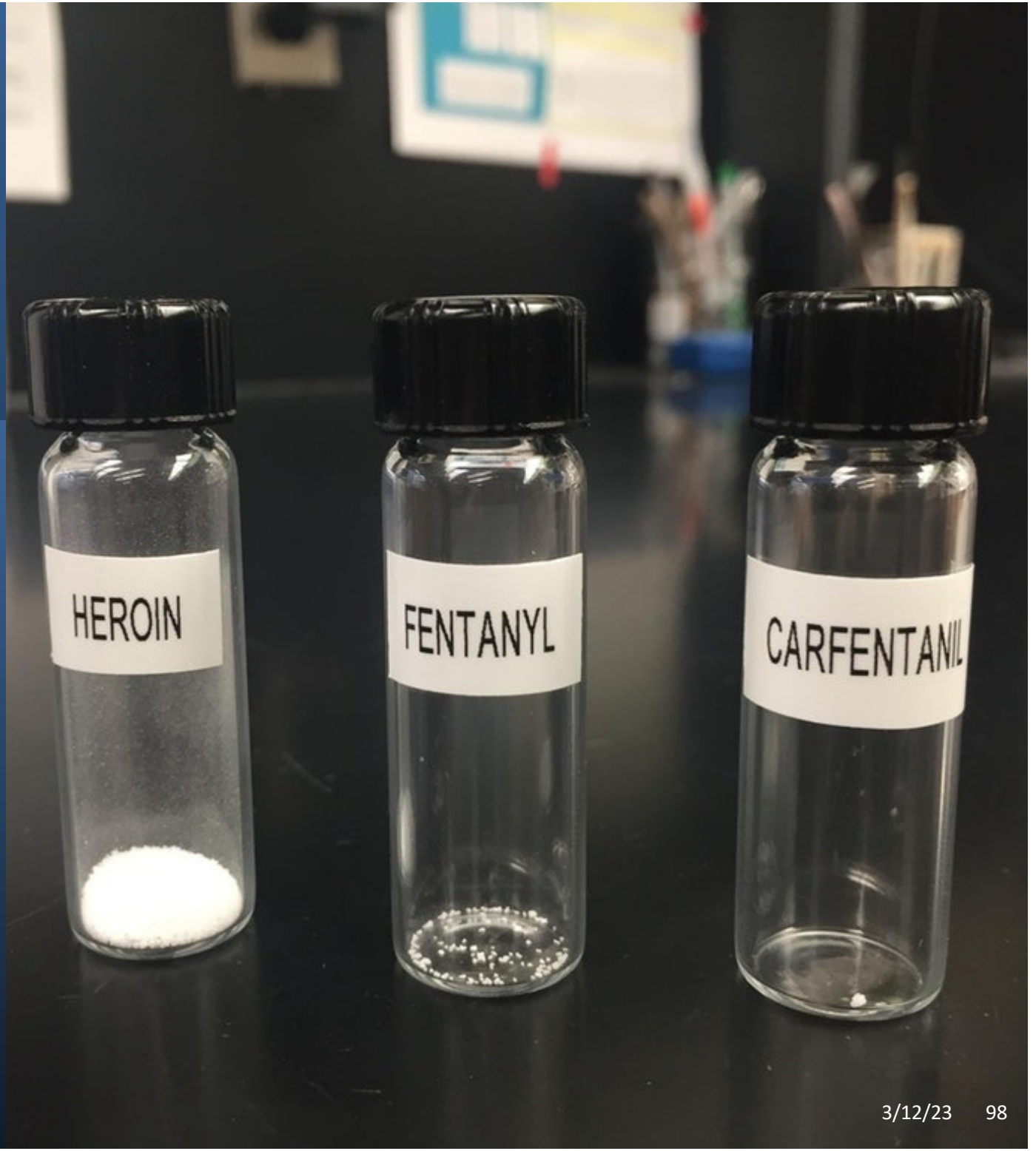
Lethal Doses of Heroin, Fentanyl, and Carfentanil



Fentanyl Related Substances

- **3-methylfentanyl**
- **3-methylthiofentanyl**
- **4-methoxy-butyryl fentanyl**
- **Acetyl norfentanyl**
- **Acetyl-alpha-methylfentanyl**
- **Acetylfentanyl**
- **Acryl-alpha-methylfentanyl**
- **Acrylfentanyl**
- **Alfentanil**
- **Alpha-methylfentanyl**
- **Alpha-methylthiofentanyl**
- **Benzodioxole fentanyl**
- **Benzoylbenzyl fentanyl**
- **Benzylfentanyl**
- **Beta-hydroxy-3-methylfentanyl**
- **Beta-hydroxyfentanyl**
- **Beta-hydroxythiofentanyl**
- **Butanoyl 4-fluoro fentanyl**
- **Butyryl fentanyl**
- **Carfentanil**
- **Crotonyl fentanyl**
- **Cyclopentyl fentanyl**
- **Cyclopropyl fentanyl**
- **Fluorobutyryl fentanyl**
- **Fluorofentanyl**
- **Fluoroisobutyryl fentanyl**
- **Furanyl fentanyl**
- **Isobutyryl fentanyl**
- **Lofentanil**
- **Methoxyacetyl fentanyl**
- **N-isobutanoyl 4-fluoro fentanyl**
- **Ortho-fluorofentanyl**
- **P-fluorobutyryl fentanyl**
- **P-fluorofentanyl**
- **P-fluoroisobutyryl fentanyl**
- **Phenyl fentanyl**
- **Remifentanil**
- **Sufentanil**
- **Tetrahydrofuran fentanyl**
- **Thenylfentanyl**
- **Thiofentanyl**
- **Thiofuranyl fentanyl**

Drug Testing for Fentanyl

Fentanyl	Actiq, Duragesic, Fentora, Lazanda, Sublimaze, Subsys, Ionsys	Plasma Detection 3–12 hrs	Urine Detection 1–3 days
Norfentanyl	Fentanyl metabolite		

Window Detection and Half Life of Fentanyl

- The mean elimination half-life is(1-3):
- -IV: 2 to 4 hours
- -Iontophoretic transdermal system (Ionsys) terminal half-life: 16 hours
- -Transdermal patch: 17 hours (13-22 hours, half-life is influenced by absorption rate)
- -Transmucosal:
- -Lozenge: 7 hours
- -Buccal tablet
- -100 to 200 mcg: 3 to 4 hours
- -400 to 800 mcg: 11 to 12 hours

Drug Testing for Fentanyl(False Negatives)

- Unless bundled *(Ask your lab!)*, opiate immunoassays will miss fentanyl, meperidine, methadone, pentazocine (Talwin), oxycodone and often hydrocodone
- Morphine: GCMS may miss it unless glucuronide hydrolyzed. Can pick up with a specific test such as a specific qualitative EIA kit such as MSOPIATE. *(Ask your lab!)*
- Opioids that are "opioid" neg: hydrocodone (unless high dose), hydromorphone, oxycodone, oxymorphone, fentanyl, methadone, buprenorphine, Demerol, tramadol (=most items rx'd)
- Illnesses that cause lactic acidosis can cause false negatives
- Patients taking opioids can be tested specifically for heroin use by looking for one of its specific metabolites): 6-monoacetyl morphine (6-MAM) duration 2-4 hours (certainly < 8) only on GCMS; positive as morphine and/or codeine for 2-3 days

Drug Testing for Fentanyl

- SAMHSA TIP 63 (pages 2-14 to 2-16) offers more information about testing and interpretations along with treatment implications.
- In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug.
- Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug.

Fentanyl and Pregnancy

- US FDA pregnancy category: C
- Maternal use of fentanyl may cause withdrawal symptoms and respiratory depression in the newborn infant.
- Every pregnancy starts out with a 3-5% chance of having a birth defect.
- This is called the background risk.
- Based on the studies reviewed, **exposure to fentanyl is not expected to increase the chance for birth defects above the background risk**.

Fentanyl and Pregnancy

- Fentanyl will usually show up on a urine test between **24-72 hours** after last use.
- Hair tests can detect the drug for up to 3 months, and blood tests can detect it between 5 and 48 hours after use depending on the dose.

Fentanyl and Pregnancy

- **Published data concerning the use of fentanyl during pregnancy consist of a small number of case reports.**
- **No congenital malformations were observed in the four reported infants exposed during the first trimester and the available data do not currently raise concerns about other adverse pregnancy outcomes or altered neurodevelopment in the child.**
- **However, data are too limited to permit an evidence-based assessment of these risks.**
- **Use of any opioid during pregnancy, particularly around the time of delivery, confers a risk of neonatal respiratory depression.**
- **Prolonged use of opioids throughout pregnancy may also result in neonatal withdrawal.**

Product Specific Information

New Formulations since 2019

- Actiq (fentanyl)-transmucosal film
- Fentora(fentanyl)-buccal tablets
- Lazanda(fentanyl)-nasal spray
- Subsys(fentanyl)-sublingual spray
- Infurmorph(morphine)– epidural injection
- Dsuvia(sufentanil)- sublingual tablets
- Conzip(tramadol)-extended release tablets
- Olinvyk (oliceridine)- IV Opioid
- Dsuvia, AcelRx (sufentanil) sublingual tablet 30 mcg

Arymo ER (Morphine Sulfate ER tablets)

- **Strengths:** 15mg, 30mg, 60mg
- **Key Instructions:**
  - Initial dose in opioid-naïve and opioid non-tolerant patients is 15mg every 8 or 12 hours
  - Dose adjustments may be done every 1 to 2 days
  - Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth

- **Dosing interval:** 8 or 12 hours
- **Drug interactions:** P-gp inhibitors can increase the exposure of morphine by about two-fold and increase risk of respiratory depression
- A single dose of 60mg, or total daily dose of 120mg, is for use in opioid-tolerant patients only

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Arymo ER (Morphine Sulfate ER tablets)

Safety Concerns:

- **Do not attempt to chew, crush, or dissolve. Swallow whole.**
- **Use with Caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen.**

Avinza (morphine Sulfate ER capsules)

- **Key Instructions:**
  - Initial dose in opioid non-tolerant patients is 30mg
  - Titrate in increments of not greater than 30mg using a minimum of 3 to 4 day intervals
  - Swallow capsule whole (do not chew, crush, or dissolve)
  - May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately
  - **Maximum daily dose: 1600mg** due to risk of serious renal toxicity by excipient, fumaric acid
- **Strengths:** 30mg, 45mg, 60mg, 75mg, 90mg, 120mg
- **Dosing:** Once a day
- **Drug interactions:**
  - Alcoholic beverages or medications containing alcohol may cause a rapid release and absorption of a potentially fatal dose of morphine
  - P-gp inhibitors may increase the absorption/exposure of morphine by about two-fold.
- 90mg and 120mg capsules are for use in opioid-tolerant patients only
- **Safety concerns:** None

Belbuca (buprenorphine buccal film)

- **Strengths:** 75mcg, 150mcg, 300mcg, 450mcg, 600mcg, 750mcg, 900mcg
- **Dosing Interval:** 12 hours (once every 24 hours for initiation in opioid naïve patients and patients taking less than 30mg oral morphine equivalents)
- Belbuca 600 mcg, 750 mcg, and 900 mcg are for use following titration from doses of Belbuca.

- **Equipotency to oral morphine has not been established**
- **Specific Drug Interactions:**
  - CYP3A4 inhibitors may increase buprenorphine levels
  - CYP3A4 inducers may decrease buprenorphine levels
  - Benzodiazepines may increase respiratory depression
  - Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointes

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Belbuca (buprenorphine buccal film)

Key Instructions:

- Opioid-naïve patients or patients taking less than 30 mg oral morphine sulfate equivalents (MSE): Initiate treatment with a 75 mcg buccal film, once daily, or if tolerated, every 12 hours.
  - Titrate 150 mcg every 12 hours no earlier than 4 days after initiation.
  - Individual titration to a dose provides adequate analgesia and minimizes adverse reactions should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days.
- When converting from another opioid, first taper the current opioid to no more than 30 mg oral MSE per day prior to initiating Belbuca.
  - If prior daily dose before taper was 30mg to 89mg oral MSE, initiate with 150 mcg dose every 12 hours.
  - If prior to daily dose before taper was 90mg to 160 mg oral MSE, initiate with 300 mcg dose every 12 hours.
  - Titration of the dose should proceed in increments of 150 mcg every 12 hours, no more than every 4 days.

Belbuca
(buprenorphine buccal film)

Key Instructions-Continued:

- **Maximum Dose: 900 mcg every 12 hours** due to the potential for QTc prolongation
- **Severe Hepatic Impairment:** Reduce the starting and incremental dose by half that of patients with normal liver function.
- **Oral Mucositis:** Reduce the starting and incremental dose by half that of patients without mucositis
- Do not use if the package seal is broken or the film is cut, damaged, or changed in any way

Safety Concerns: QTc prolongation and torsade de pointes

- Hepatotoxicity

Butrans
(buprenorphine transdermal system)

- **Drug Interactions:**
  - CYP3A4 inhibitors may increase buprenorphine levels
  - CYP3A4 inducers may decrease buprenorphine levels
  - Benzodiazepines may increase respiratory depression
  - Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointes
- **Strengths:** 5mcg/hr, 7.5mcg/hr, 10 mcg/hr, 15mcg/hr, 20 mcg/hr
- **Dosing Interval:** One transdermal system every 7 days.
- Equipotency to oral morphine has not been established.
- 7.5mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr transdermal systems are for opioid-tolerant patients only.

Butrans
(buprenorphine transdermal system)

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Key Instructions:

- Initial dose in opioid non-tolerant patients when converting from less than 30 mg MSE, and in mild to moderate hepatic impairment is 5 mcg/hr dose.
- When converting from 30 to 80 MSE first taper to 30 MSE, then initiate with 10 mcg/hr dose.
- Titrate in 5 mcg/hr or 10 mcg/hr increments by using no more than 2 patches of the 5 mcg/hr or 10 mcg/hr system(s) with a minimum of 72 hours between dose adjustments. The total dose from all patches should not exceed 20 mcg/hr
- **Maximum dose: 20 mcg/hr** due to risk of QTc prolongation.

Butrans (buprenorphine transdermal system)

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Key Instructions-Continued:

- **Application:**
  - Apply only to sites indicated in the Full Prescribing Information.
  - Apply to intact/non-irritated skin.
  - Skin may be prepared by clipping hair, washing site with water only
  - Rotate site of application, wait a minimum of 3 weeks before reapplying to the same site.
  - **Do Not Cut**
- Avoid exposure to heat
- Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
- **Safety Concerns:**
  - QTc prolongation and torsade de pointe.
  - Hepatotoxicity.

Butrans
(buprenorphine transdermal system)

Safety Concerns:

QTc prolongation and torsade de pointe.

Hepatotoxicity.

Application site reactions.

Dolophine (methadone HCL tablets)

- **Strengths:** 5 mg and 10 mg
- **Dosing Interval:** 8 to 12 hours
- Refer to full prescribing information for use in opioid-tolerant patients.
- Equipotency to oral morphine varies depending on patient's prior opioid experience.
- **Drug Interactions:**
- Pharmacokinetic drug-drug interactions with methadone are complex.
  - CYP450 inducers may decrease methadone levels.
  - CYP450 inhibitors may increase methadone levels.
  - Anti-retroviral agents have mixed effects on methadone levels.
- Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe.
- Benzodiazepines may increase respiratory depression.

Dolophine (methadone HCL tablets)

Key Instructions:

- Initial dose in opioid non-tolerant patients is: 2.5 to 10mg
- Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information.
- Titrate slowly, with dose increases no more frequent than every 3 to 5 days. Because of high variability in methadone metabolism, some patients may require substantially longer periods between dose increases (up to 12 days).
- High inter-patient variability in absorption, metabolism, and relative analgesic potency.
- Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec. 8)

Dolophine (methadone HCL tablets)

Safety Considerations:

- QTc prolongation and torsade de pointe.
- Peak respiratory depression occurs later and persists longer than analgesic effect.
- Clearance may increase during pregnancy.
- False positive urine drug screens possible.

Duragesic (fentanyl transdermal system)

- **Strengths:** 12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr (*These strengths are only available in generic form)
- **Dosing interval:** Every 72 hours.
- See individual product information for conversion recommendations from prior opioid
- All doses of Duragesic are indicated for use in opioid-tolerant patients only.

- **Drug interactions:**
  - CYP3A4 inhibitors may increase fentanyl exposure.
  - CYP3A4 inducers may decrease fentanyl exposure.
  - Discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration.

Duragesic (fentanyl transdermal system)

Key Instructions:

- Use product specific information for dose conversion from prior opioid
- Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment
- **Application:** Apply to intact/non-irritated/non-irradiated skin on a flat surface.
  - Skin may be prepped by clipping hair, washing site with water only
  - Rotate application site.
  - Titrate using a minimum of 72 hour intervals between dose adjustments.
  - Do Not Cut

Duragesic (fentanyl transdermal system)

Key Instructions- Continued:

- Avoid exposure to heat.
- Avoid accidental contact when holding or caring for children.
- Dispose of used/unused patches by folding adhesive side together and flushing down the toilet.

Contraindications:

- Patients who are not opioid-tolerant.
- Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time.
- Management of post-operative pain, including use after out-patient or day surgery.
- Management of mild pain.

Duragesic (fentanyl transdermal system)

Safety Concerns:

- Accidental exposure due to secondary exposure to unwashed/unclothed application site.
- Increased drug exposure with increased core body temperature or fever.
- Bradycardia
- Application site skin reactions.

Embeda (morphine sulfate ER-naltrexone capsules)

- **Strengths:** 20mg/0.8mg, 30mg/1.2mg, 50mg/2mg, 60mg/2.4mg, 80mg/3.2mg, 100mg/4mg
- **Dosing interval:** Once a day or every 12 hours.
- Embeda 100mg/4mg capsule is for use in opioid-tolerant patients only.
- Safety Concerns: None

- **Drug Interactions:**
  - Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine sulfate.
  - P-gp inhibitors may increase the absorption/exposure of morphine sulfate by about two-fold.

Embeda (morphine sulfate ER-naltrexone capsules)

Key Instructions:

- Intial dose as first opioid: 20mg/0.8mg.
- Titrate using a minimum of 1 to 2 day intervals.
- Swallow capsules whole (do not chew, crush, or dissolve)
- Crushing or chewing will release morphine, possibly resulting in a fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms.
- May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.

Exalgo (hydromorphone HCl ER tablets)

- **Strengths:** 8mg, 12mg, 16mg, 32mg
- **Dosing Interval:** Once a day.
- Drug Interactions**:** None
- All doses of Exalgo are indicated for opioid-tolerant patients only.
- **Adverse Reactions:** Allergic manifestations to sulfite component.

- Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.
- Key Instructions:
  - Use the conversion ratios in the product information.
  - Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal renal function.

Exalgo (hydromorphone HCl ER tablets)

Key Instructions-Continued

- Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal renal function.
- Titrate in increments of 4 to 8 mg using a minimum of 3 to 4 day intervals
- Swallow tablets whole (do not chew, crush, or dissolve).
- Do not use in patients with sulfite allergy- contains sodium metabisulfite.

Hysingla ER (Hydrocodone bitartrate ER tablets)

- **Strengths:** 20mg, 30mg, 40mg, 60mg, 80mg, 100mg, 120mg
- **Dosing Interval:** Every 24 hours
- A single dose of Hysingla ER greater than or equal to 80 mg is only for use in opioid tolerant patients.
- See individual product information for conversion recommendations from prior opioid
- **Drug Interactions:**
  - CYP3A4 inhibitors may increase hydrocodone exposure.

- **Drug Interactions-** Continued**:**
  - CYP3A4 indicers may decrease hydrocodone exposure.
  - Concomitant use of Hysingla ER with strong laxatives (e.g. Lactulose) that rapidly increase GI motility may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels.
  - The use of MAOIs or tricyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER.

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Hysingla ER (Hydrocodone bitartrate ER tablets)

Key Instructions:

- Opioid-naïve patients: initiate treatment with 20mg orally once daily. During titration, adjust the dose in increments of 10mg to 20 mg every 3 to 5 days until adequate analgesia is achieved.
- Swallow tablets whole (do not chew, crush, or dissolve).
- Consider use of an alternative analgesic in patients who have difficulty swallowing or have underlying gastrointestinal disorders that may predispose them to obstruction.
- Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
- Use ½ of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation, when administering Hysingla ER to patients with severe hepatic impairment or patients with moderate to severe renal impairment.

Hysingla ER (Hydrocodone bitartrate ER tablets)

Safety Concerns:

- Use with caution in patients with difficulty swallowing the tablet or underlying gastrointestinal disorders that may predispose patients to obstruction.
- Esophageal obstruction, dysphagia, and choking have been reported with Hysingla.
- In nursing mothers, discontinue nursing or discontinue drug.
- QTc prolongation has been observed with Hysingla ER following daily doses of 160mg. Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. In patients who develop QTc prolongation, consider reducing the dose.

Kadian (morphine sulfate ER capsules)

- **Strengths:** 10mg, 20mg, 30mg, 40mg, 50mg, 60mg, 70mg, 80mg, 100mg, 130mg, 150mg, 200mg
- **Dosing Interval:** Once a day or every 12 hours.
- Kadian 100mg, 130mg, 150mg, and 200mg capsules are for use in opioid-tolerant patients only.
- Safety Concerns: None

- Drug Interactions:
  - Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine sulfate.
  - P-gp inhibitors may increase the absorption/exposure of morphine sulfate by about two-fold.

Kadian (morphine sulfate ER capsules)

Key Instructions:

- Product information recommends not using as first opioid.
- Titrate using a minimum of 2-day intervals.
- Swallow capsules whole (do not chew, crush, or dissolve).
- May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.

Kloxxado (Naloxone)

The U.S. Food and Drug Administration announced today the approval of a higher dose naloxone hydrochloride nasal spray product to treat opioid overdose.

The newly approved product delivers 8 milligrams (mg) of naloxone into the nasal cavity.

The FDA had previously approved 2 mg and 4 mg naloxone nasal spray products.

MorphaBond ER (morphine sulfate ER tablets)

- **Strengths:** 15mg, 30mg, 60mg, 100mg
- **Dosing interval:** Every 12 hours.
- **Drug Interactions:** P-gp inhibitors may increase the absorption/exposure of morphine sulfate by about two-fold.
- Safety Concerns: None
- MorphaBond ER 100mg tablets, as single dose greater than 60mg, or a total daily dose greater than 120mg, are only for use in patients in whom tolerance to an opioid of comparable potency has been established.

Key Instructions:

- For opioid-naïve and opioid non-tolerant patients, initiate treatment with 15mg tablets orally every 12 hours.
- Swallow tablets whole (do not cut, break, chew, crush, or dissolve).

MS Contin (morphine sulfate ER tablets)

- **Strengths:** 15mg, 30mg, 60mg, 100mg, 200mg
- **Dosing Interval:** Every 8 hours or Every 12 hours
- **Drug Interactions:** P-gp inhibitors may increase the absorption/exposure of morphine sulfate by about two-fold.
- MS Contin 100mg and 200mg tablet strengths are for use in opioid-tolerant patients only.

- Safety Concerns: None
- **Key Instructions:**
  - Product information recommends not using as first opioid.
  - Titrate using a minimum of 1 to 2-day intervals.
  - Swallow tablets whole (do not chew, crush, or dissolve).

Nucynta ER (tapentadol HCl ER tablets)

- **Strengths:** 50mg, 100mg, 150mg, 200mg, 250 mg
- **Dosing Interval:** Every 12 hours.
- No specific considerations for opioid-tolerant patients.
- Equipotency to oral morphine has not been established.
- **Drug Interactions:** Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of taperntadol.
- Contraindicated in patients taking MAOIs.

Nucynta ER (tapentadol HCl ER tablets)

Key Instructions:

- Use 50 mg every 12 hours as initial dose in opioid non-tolerant patients
- Titrate by 50 mg increments using a minimum of 3-day intervals.
- **Maximum total daily dose is 500mg**
- Swallow tablets whole (do not chew, crush, or dissolve).
- Take one tablet at a time and with enough water to to ensure complete swallowing immediately after placing in the mouth.
- Dose once daily in moderate hepatic impairment with 100 mg per day maximum.
- Avoid use in severe hepatic and renal impairment.

Nucynta ER (tapentadol HCl ER tablets)

Safety Considerations:

- Risk of serotonin syndrome
- Angioedema

Opana ER (oxymorphone HCl ER tablets)* voluntarily removed from the market in June 2017

- **Strengths:** 5mg, 7.5mg, 10mg, 15mg, 20mg, 30mg, 40mg
- **Dosing Interval:** Every 12 hours, some may benefit from asymmetric dosing (different dose in AM and PM)
- **Drug Interactions:** Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.

- There are no product considerations for use in opioid-tolerant patients.
- Approximately 3:1 oral morphine to oxymorphone oral dose ratio.
- **Key Instructions:** Use 5mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance <50 mL/min) and patients over age 65.

Opana ER (oxymorphone HCl ER tablets)

Key Instructions- continued**:**

Swallow tablets whole (do not chew crush, or dissolve).

Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in mouth.

Titrate in increments of 5 to 10mg using a minimum of 3 to 7-day intervals.

Contraindicated in moderate to severe hepatic impairment.

Opana ER (oxymorphone HCl ER tablets)

- Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen.

OxyContin (oxycodone HCl ER tablets)

- **Strengths:** 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg
- **Dosing interval:** Every 12 hours.
- **Drug Interactions:**
  - CYP3A4 inhibitors may increase oxycodone exposure.
  - CYP3A4 inducers may decrease oxycodone exposure.
- Approximately 2:1 oral morphine to oxycodone oral dose ratio.

Opioid-tolerant considerations:

- Adults:
  - Single dose greater than 40mg or total daily dose greater than 80mg are for use in adult patients in whom tolerance to a comparably potent opioid is established.

OxyContin (oxycodone HCl ER tablets)

Opioid-tolerant considerations- Continued:

Pediatric Patients (age:≥ 11):

- For use only in **opioid-tolerant** pediatric patients already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20mg per day oxycodone or its equivalent for at least 2 days immediately preceding dosing with OxyContin.
- If needed, pediatric dosage may be adjusted in 1 to 2 day intervals.
- When a dose increase is clinically indicated, the total daoly oxycodone dose usually can be increased by 25% of the current total daily dose.

OxyContin (oxycodone HCl ER tablets)

Key instructions:

For Adults:

- Initial dose in opioid-naïve and opioid non-tolerant patients is 10mg every 12 hours.
- If needed, adult dosage may be increased in 1 to 2 day intervals.
- When a dose increase is clinically indicated, the total daily dose can be increased by 25% to 50% of the current dose.

For Pediatric patients: Use only in **opioid-tolerant** patients.

For all Patients:

- Hepatic impairment: start with one third to one half the usual dosage

OxyContin (oxycodone HCl ER tablets)

Key instructions- Continued:

For all Patients:

- Hepatic impairment: start with one third to one half the usual dosage
- Renal impairment (creatinine clearance <60mL/min): start with one half the usual dosage.
- Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve).
- Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.

OxyContin (oxycodone HCl ER tablets)

Safety Concerns:

- Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet.
- **Contraindicated in patients with gastrointestinal obstruction.**

Targiniq ER (oxycodone HCl/ naloxone HCl ER tablets)

- **Strengths:** 10mg/5mg, 20mg/10mg, 40mg/20mg
- **Dosing interval:** Every 12 hours.
- **Drug Interactions:**
  - CYP3A4 inhibitors may increase oxycodone exposure.
  - CYP3A4 inducers may decrease oxycodone exposure.
- See individual product information for conversion recommendations from prior opioid.

- Single dose greater than 40mg/2mg or total daily dose of 80mg/40mg are for use in opioid-tolerant patients only.
- **Safety Concerns: Contraindicated in patients with moderate to severe hepatic impairment.**

Targiniq ER (oxycodone HCl/ naloxone HCl ER tablets)

Key Instructions:

- Opioid-naïve patients: initiate treatment with 10mg/5mg every 12 hours.
- Titrate using a minimum of 1 to 2 day intervals.
- DO NOT EXCEED 80mg/40mg total daily dose (40mg/20mg every 12 hours) of Targiniq ER.
- May be taken with or without food.
- Swallow tablets whole. Do not chew, ccrush, split, or dissolve, as this will release oxycodone, possibly resulting in fatal overdose, and maloxone, possibly reslting in withdrawal symptoms.

Targiniq ER (oxycodone HCl/ naloxone HCl ER tablets)

Key Instructions-Continued:

- Hepatic impairment: **contraindicated in moderate and severe hepatic impairment.** In patients with mild hepatic impairment, start with ine third to one half the usual dosage.
- Renal impairment (creatinine clearance <60mL/min): start with one half the usual dosage.

Troxyca ER (oxycodone HCl- naltrexone capsules)

- **Strengths:** 10mg/1.2mg, 20mg/2.4mg, 30mg/3.6mg, 40mg/4.8mg, 60mg/7.2mg, 80mg/9.6mg
- **Dosing interval:** Every 12 hours.
- **Drug interactions:**
  - CYP3A4 inhibitors may increase oxycodone exposure.
  - CYP3A4 inducers may decrease oxycodone exposure.
- Single doses greater than 40mg/4.8mg, or total daily dose greater than 80mg/9.6mg are only for use in opioid-tolerant patients only.
- Safety concerns: None
- See individual product information for conversion recommendations from prior opioid.

Troxyca ER (oxycodone HCl-naltrexone capsules)

Key Instructions:

- Opioid-naïve and opioid non-tolerant patients: 10mg/1.2mg, every 12 hours
- Total daily dose may be adjusted by 20mg/2.4mg every 2 to 3 days as needed
- Swallow capsule whole (do not chew, crush, or dissolve).
- Crushing, chewing, or dissolving will release oxycodone, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms.
- For patients that have difficulty swallowing, Troxyca ER, can also be taken by sprinkling the capsule contents (pellerts) on applesauce and swallowing immediately without chewing.
- Do not administer Troxyca ER pellets through a nasogastric or gastric tube

Vantrela ER (hydrocodone bitartrate ER tablets)

- **Strength:** 15mg, 30mg, 45mg, 60mg, 90mg
- **Dosing interval:** Every 12 hours.
- **Drug interactions:**
  - CYP3A4 inhibitors may increase hydrocodone exposure.
  - CYP3A4 inducers may decrease hydrocodone exposure.
- **Safety Concerns:** None
- A 90mg tablet or a single dose greater than 60mg, or a total daily dose greater than 120mg are for use in opioid-tolerant patients only.
- See individual product information for conversion recommendations from prior opioid.

Vantrela ER (hydrocodone bitartrate ER tablets)

- Opioid naïve and opioid non-tolerant patients: initiate with 15mg every 12 hours. Dose can be increased from the current dose to the next higher dose every 3 to 7 days as needed.
- Swallow tablets whole (do not chew, crush, or dissolve).
- Mild or moderate hepatic and moderate to severe renal impairment: Initiate therapy with ½ of the recommended initial dose in patients with either if these impairments, if a dose less than 15mg is needed, use alternative analgesic options.

Xtampza ER (oxycodone ER capsules)

- **Strengths:** 9mg, 13.5mg, 18mg, 27mg, 36mg (strengths are equivalent to 10mg, 15mg, 20mg, 30mg, and 40mg oxycodone HCl, respectively)
- **Dosing interval:** Every 12 hours.
- **Drug interactions:**
  - CYP3A4 inhibitors may increase oxycodone exposure.
  - CYP3A4 inducers may decrease oxycodone exposure.
- A single dose greater than 36mg or a total daily dose greater than 72mg is for use in opioid-tolerant patients only.
- **Safety Concerns:** none.
- There are no established conversion ratios for conversion from other opioids to Xtampza ER defined by clinical trials.

Xtampza ER (oxycodone ER capsules)

Key Instructions:

- Opioid naïve and opioid non-tolerant patients: Initiate with 9mg every 12 hours.
- Titrate using a minimum of 1 to 2 day intervals.
- Take Xtampza ER capsules with the same amount of food in order to ensure consistent plasma levels are achieved.
- Maximum daily dose: 288mg (8x36mg capsules) because the safety of excipients has not been established for higher doses
- For patients that have difficulty swallowing, Xtampza ER can also be taken by sprinkling the capsule contents on soft foods or into a cup and then administering directly into the mouth and swallowing immediately. Xtampza ER may also be administered through a gastrostomy or nasogastric feeding tube.
- Hepatic impairment: Initiate therapy at 1/3 to ½ the usual dosage
- Renal impairment (creatinine clearance <60mL/min): Follow a conservative approach to dose initiation and adjust according to the clinical situation.

Zohydro ER (hydrocodone bitartrate ER capsules)

- **Strength:** 10mg, 15mg, 20mg, 30mg, 40mg, 50mg
- **Dosing interval:** Every 12 hours
- Single dose greater than 40mg or total daily dose greater than 80mg are for use in opioid-tolerant patients only.
- **Safety Concerns:** None
- Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.
- **Key Instructions:**
  - Initial dose in opioid non-tolerant patients is 10mg.
  - Titrate in increments of 10mg using a minimum of 3 to 7 day intervals.
  - Swallow capsule whole (do not chew, crush, or dissolve).
- **Drug interactions:**
  - Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone.
  - CYP3A4 inhibitors may increase hydrocodone exposure.
  - CYP3A4 inducers may decrease hydrocodone exposure.

Additional Information

www.dailymed.nlm.nih.gov –DailyMed

www.fda.gov/drugsatfda -Drugs@FDA

CDC Guidelines for Prescribing Opioids for Chronic Pain

- **Nonopioid therapies include:**
- Nonopioid medications such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and selected antidepressants and anticonvulsants
- Physical treatments (e.g., heat therapy, acupressure, spinal manipulation, remote electrical neuromodulation, massage, exercise therapy, weight loss)
- Behavioral treatment (e.g., cognitive behavior therapy, mindfulness-based stress reduction)
- **Nonopioid therapies are at least as effective as opioids** for many common types of acute pain.
- Clinicians should **maximize use of nonpharmacologic and nonopioid pharmacologic therapies** as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient.
- Before prescribing opioid therapy for acute pain, **clinicians should discuss with patients the realistic benefits and known risks of opioid therapy**.

CDC Guidelines for Prescribing Opioids for Chronic Pain

- **Nonopioid therapies are preferred for subacute and chronic pain.**Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and **only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks** to the patient.
- Before starting opioid therapy for subacute or chronic pain, **clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued** if benefits do not outweigh risks.

CDC Guidelines for Prescribing Opioids for Chronic Pain

- When starting opioid therapy for acute, subacute, or chronic pain, **clinicians should prescribe immediate-release opioids** instead of extended-release and long-acting (ER/LA) opioids.
- **Immediate-release opioids**: faster acting medication with a shorter duration of pain-relieving action. Examples include morphine, oxycodone, or hydrocodone.
- **Extended-release and long-acting opioids**: slower acting medication with a longer duration of pain-relieving action. Examples include methadone, transdermal fentanyl, or extended-release versions of opioids such as oxycodone, hydromorphone, hydrocodone, and morphine.

CDC Guidelines for Prescribing Opioids for Chronic Pain

- When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe **the lowest effective dosage.**
- If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should **carefully evaluate individual benefits and risks when considering increasing dosage,** and should **avoid increasing dosage** above levels likely to yield diminishing returns in benefits relative to risks to patients.

CDC Guidelines for Prescribing Opioids for Chronic Pain

- For patients already receiving opioid therapy, clinicians should **carefully weigh benefits and risks and exercise care when changing opioid dosage.**
- If *benefits outweigh risks* of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy.
- If *benefits do not outweigh risks* of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to **gradually taper to lower dosages** or, if warranted based on the individual circumstances of the patient, appropriately taper and discontinue opioids.
- Unless there are indications of a life-threatening issue such as warning signs of impending overdose (e.g., confusion, sedation, or slurred speech), **opioid therapy should not be discontinued abruptly, and clinicians should not rapidly reduce opioid dosages from higher dosages.**

CDC Guidelines for Prescribing Opioids for Chronic Pain

- When opioids are needed for acute pain, clinicians should **prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.**

CDC Guidelines for Prescribing Opioids for Chronic Pain

- Clinicians should **evaluate benefits and risks with patients within 1–4 weeks** of starting opioid therapy for subacute or chronic pain or of dosage escalation.
- **Clinicians should regularly reevaluate benefits and risks of continued opioid therapy** with patients.

CDC Guidelines for Prescribing Opioids for Chronic Pain

- Before starting and periodically during continuation of opioid therapy, **clinicians should evaluate risk for opioid-related harms and discuss risk with patients.**
- Clinicians should work with patients to incorporate into the management plan **strategies to mitigate risk**, including offering naloxone.
- **Additional Strategies to Mitigate Risk**
- Ask patients about their drug and alcohol use and use validated tools or consult with behavioral specialists to screen for and assess mental health and substance use disorders.
- Use PDMP data and toxicology screening as appropriate to assess for concurrent controlled substance use that might place patients at higher risk for opioid use disorder and overdose.

CDC Guidelines for Prescribing Opioids for Chronic Pain

- When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should **review the patient's history of controlled substance prescriptions** using state prescription drug monitoring program (PDMP) data **to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose.**

CDC Guidelines for Prescribing Opioids for Chronic Pain

- When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of **toxicology testing** to **assess for prescribed medications as well as other prescribed and nonprescribed controlled substances.**

CDC Guidelines for Prescribing Opioids for Chronic Pain

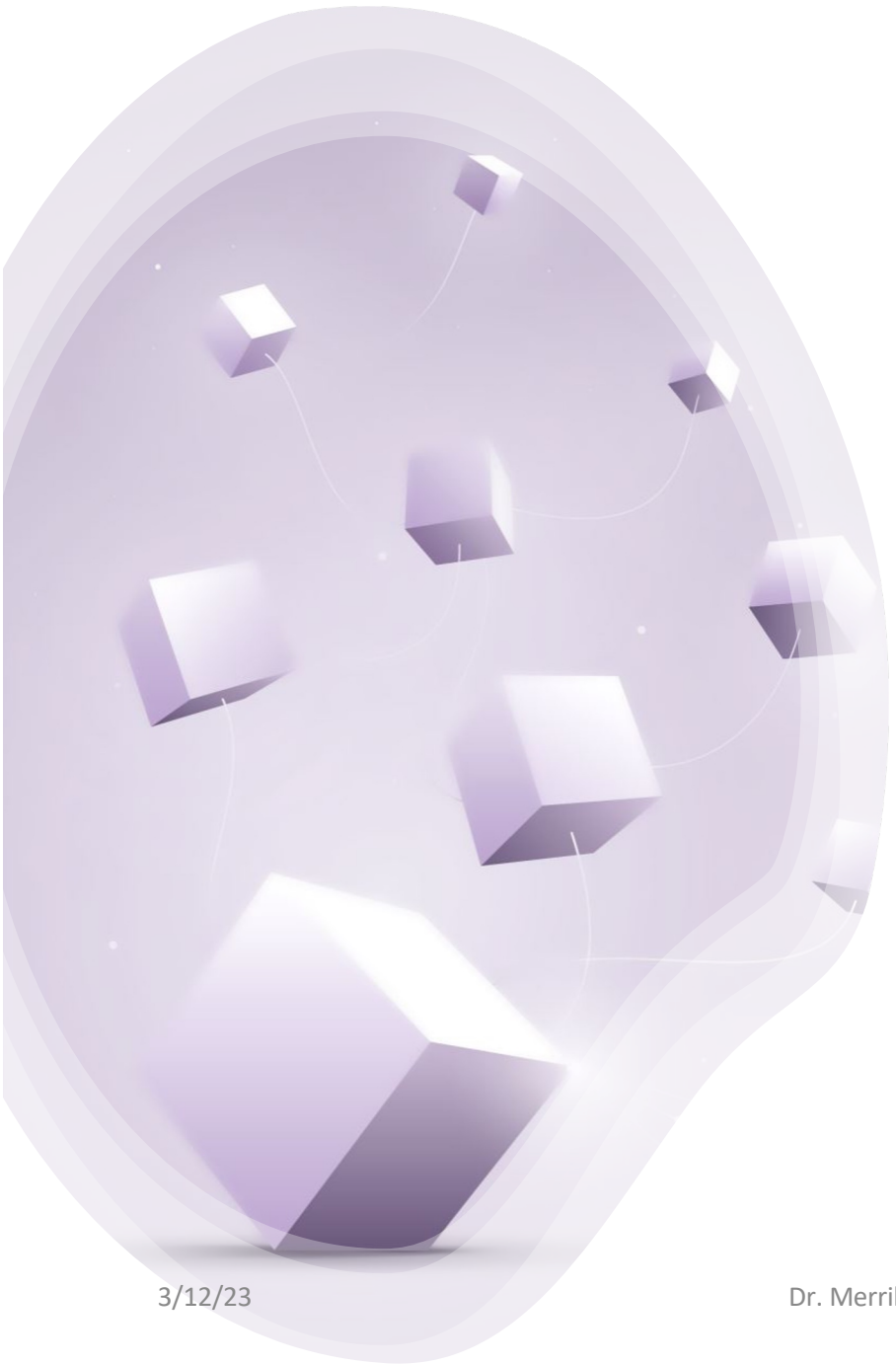
- Clinicians should use particular **caution when prescribing opioid pain medication and benzodiazepines concurrently** and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants.

CDC Guidelines for Prescribing Opioids for Chronic Pain

- **Clinicians should offer or arrange treatment with evidence-based medications** to treat patients with opioid use disorder.
- **Detoxification on its own**, without medications for opioid use disorder, **is not recommended** for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death.

CDC Guidelines for Prescribing Opioids for Chronic Pain

- **FDA-approved medications indicated for the treatment of opioid use disorder include buprenorphine, methadone, and naltrexone.**
- **Information about qualifications and the process to prescribe buprenorphine are available from the Substance Abuse and Mental Health Services Administration.**



CDC Clinical Practice Guideline for Prescribing Opioids for Pain 2022

Determining When to Initiate or Continue Opioids for Chronic Pain

- The first three CDC guidelines target determining when to initiate or continue opioid treatment.
- Nonpharmacological and pharmacological nonopioid therapies are always preferred to opioid use.
- Before ever initiating opioid therapy for chronic pain treatment goals for pain management should be set and termination strategy for safely ending opioid treatment should be developed.
- During this process and periodically during therapy providers should discuss the risks and dangers of opioid therapy with the patient. It is important to periodically do this during treatment since these risks and dangers increase the longer treatment continues.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

- Guidelines 4 through 7 address the selection of a specific opioid, as well as the dose and length of treatment including follow ups and discontinuation.
- Initial treatment in opioid nontolerant patients should always be with immediate release products at the lowest effective dose. Avoid doses of 90MME or greater and use caution with doses greater than or equal to 50MME.
- Long term chronic use often starts with treatment for acute conditions. Treatment for longer than 7 days will rarely be needed and as such quantities should be limited to only the estimated time of need.
- Providers should evaluate the benefit and harm of treatment with 1 week to 1 month of starting treatment or increasing a dose.

Assessing Risk and Addressing Harms of Opioid Use

- Guidelines 8 through 12 address minimization of risks and harms of opioid use.
- Physicians should incorporate risk assessment and reduction strategies for opioid-harm into opioid therapy and continue to periodically reassess through the duration of the therapy.
- Special attention to risk mitigation should be given to patients with: Sleep-breathing disorders, pregnant women, renal or hepatic insufficiency, over age 65, mental health conditions, substance use disorder, or a history of overdoses.
- Prescribers should utilize PDMP to monitor for doctor shopping and dangerous opioid combinations, checks should be done from every prescription to every 3 months.

Assessing Risk and Addressing Harms of Opioid Use

- Drug testing should be considered before starting and annually while continuing therapy opioid therapy to monitor for prescribed medications and illicit substances.
- Avoid concurrent prescribing of opiates and benzodiazepines if at all possible.
- Clinicians should offer or arrange for treatment of patients that develop opioid use disorder. It is possible for prescribers to undergo training and receive a waiver to provide treatment buprenorphine treatments from Substance Abuse and Mental Health Services Administration (SAMHSA). More information on the training is available from SAMHSA.

Patient Counseling

- Prescribers should council patients and care givers on the dosing regimen, how to handle missed doses, and what to do if the desired affect is not achieved.
- Prescribers should instruct patients as to the dangers associated with the use of the medication in regards to abuse and misuse potential.
- Additionally prescribers should caution patients as to possible synergistic or additive effects of medication co-use with applicable drug categories. I.e. Use of opioids and benzodiazepines.

Patient Counseling

- Prescribers should counsel patients that sharing medications with others or using them other than as directed can have serious consequences, including death, permanent damage, and adverse legal consequences.
- Prescribers should council about common side effects and what to do in case of serious adverse reactions.
- Additionally patients and care givers should be counseled about the proper safe storage of medications and unfilled prescriptions. Storage should be on par with safe storage of firearms and other dangerous objects in homes with children or others at risk of abuse or misuse of Rx medications.