Safe Prescribing of Controlled Substances

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Safe Prescribing of Controlled Substances
Part 1

Objectives

- Describe federal guidelines related to prescribing Schedules 1-5 medications
- Discuss common examples and safety issues related to prescribing Schedules 2-5 medications
- Develop strategies for avoidance of common medication errors when prescribing Schedule 2 -5 medications

Practitioner's Manual

www.deadiversion.usdoj.gov

DEA's responsibility is to make sure that drugs are not diverted for illicit purposes.

Mrs. Boudreaux

Mrs. Boudreaux has chronic low back pain. She takes hydrocodone when she has bad "pain days". Mrs. Boudreaux gets good pain relief and and takes her meds as prescribed. She's never called in early for a refill, she keeps her appointments with pain med provider, and she's been compliant with all urine drug screens as part of her pain provider's protocol.

Mrs. Boudreaux's Adult Daughter

- Injures her back pushing her lawn mower. It's a weekend. She is in a lot of pain and can't get relief from 800 mg ibuprofen
- Mrs. Boudreaux gives her daughter one of her Lortab so she can sleep tonight

Is this an example of Diversion?

DEA's responsibility is to make sure that drugs are not diverted for illicit purposes.

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Federal Law: Title 21 of the Code of Federal Regulations, Sections 1308.11- 1308.15 places controlled substances into schedules

Drug Abuse Prevention and Control Act

- **Passed by 91st US Congress in 1970, enacted May 1, 1971**
- **Title II of the Comprehensive Drug Abuse Prevention and Control Act**
- **Signed into law by Richard Nixon**

Controlled Substances Act (CSA)

PURPOSE:

- **Decrease drug abuse and dependence**
- **Regulates sale, production, purchase and use of certain drugs**
- *****Classify drugs to help law enforcement and medical community to understand it's nature**

Drug Enforcement Agency

- **DEA created in 1973**

Controlled Substances

Why are they controlled?

Controlled Substances are divided into 5 Schedules

- Schedule I
- Schedule II
- Schedule III
- Schedule IV
- Schedule V

What's "Schedule I" mean?

- Has absolutely NO medical value
- There is a lack of accepted safety for use under medical supervision
- High potential for abuse

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

Schedule I

Examples:

- Heroin
- LSD
- Peyote
- Ecstasy
- Marijuana

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

What about Medical Marijuana?

- Medical Marijuana is legal in 33 states and DC
- FDA indication for seizures

Medical Marijuana?

- June 21, 2011
- Petition to FDA to move marijuana from schedule I to III,IV, V

Medical Marijuana?

- Petition refused after DHHS evaluation of all relevant data because:

1. "marijuana has a high potential for abuse"

deadiversion.usdoj.gov Federal Register Volume 76, Number 131 (Friday, July 8, 2011)]
[Pages 40552-40589]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2011-16994]

Medical Marijuana?

2. Marijuana has no currently accepted medical use in treatment in the US b/c

- **"drug's chemistry is not known and reproducible";**
- **"there are no adequate safety studies";**
- **"there are no adequate and well controlled studies proving efficacy"**
- **"the drug is not accepted by qualified experts"**
- **"the scientific evidence is not widely available"**

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Medical Marijuana?

3. Marijuana lacks accepted safety for use under medical supervision.

- **"No FDA approved marijuana products"**
- **"Marijuana not under a New Drug Application (NDA) evaluation at FDA for any indication"**
- **"does not have a currently accepted medical use in treatment in the US or a currently accepted medical use with severe restrictions"**
- **"the known risks have not been shown to be outweighed by specific benefits in well controlled clinical trials that scientifically evaluate safety and efficacy"**

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True or False

DEA allows prescription of heroin and LSD.

Why does the DEA allow some prescription of Schedule I drugs?

Why does the DEA allow some prescription of Schedule I drugs?

- **Bona fide research!**
- **Provided the researcher is deemed to be qualified and competent, and the researcher's protocol is deemed to be meritorious**

What's "Schedule II" mean?

- **High potential for abuse with severe psychological or physical dependence**

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

Schedule II

Examples:

- Hydromorphone (Dilaudid)
- Methadone (Dolophine)
- Meperidine (Demerol)
- Oxycodone (Oxycontin)
- Fentanyl (Sublimaze or Duragesic)

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

Other Schedule II, Non-narcotics

Examples:

- Amphetamine (Dexedrine, Adderall)
- Methamphetamine (Desoxyn)
- Methylphenidate (Ritalin)
- Cocaine

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

Is there a Medical Use for Cocaine?

1. Yes
2. No

What's the Medical Use for Cocaine?

- Anesthesia: used as a mucosal anesthetic in nostrils, TM
- Epistaxis

What's the Medical Use for Cocaine?

- Cocaine oronasolaryngeal
- 4%, 10% solution

What's Schedule III mean?

- May lead to moderate or low physical dependence or high psychological dependence

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

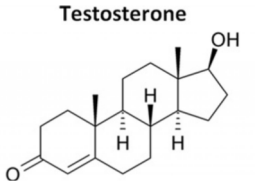
Schedule III Examples

- Anabolic steroids (testosterone)
- Codeine/hydrocodone with aspirin or acetaminophen
- Buprenorphine
- Ketamine
- Marinol
- Short acting barbiturates (act as CNS depressants)

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

Testosterone

- Testosterone is a hormone essential for the growth and development of male sex organs and maintenance of secondary male characteristics (Ex. facial hair)



FDA Approved Use of Testosterone

- FDA approved only for men who have low testosterone levels caused by "certain medical conditions"
- Disorders of the testicles, pituitary gland, or brain that cause hypogonadism
- Not approved for enhancement of athletic performance
- Aging isn't a "medical condition"

Aging and Low T

- As men age, testosterone levels decrease

Age	Total Testosterone (ng/dl)	Free Testosterone (ng/dl)	SHBG (nmol/L)
25-43	617	12.3	35.5
35-44	668	10.3	40.1
45-54	606	9.1	44.6
55-64	562	8.3	45.5
65-74	524	6.9	48.7
75-84	471	6.0	51
85-100	376	5.4	65.9

Testosterone

- Approximately 70% of men who receive testosterone prescriptions through retail pharmacies are between 40 and 64 years old
- The most common diagnostic code: non-specific diagnosis of "testicular hypofunction, not elsewhere classified"

[03-03-2015] The U.S. Food and Drug Administration (FDA)

Testosterone

- A diagnosis of hypogonadism requires laboratory evidence of low testosterone levels measured on at least two separate mornings

[03-03-2015] The U.S. Food and Drug Administration (FDA)

Testosterone Use

- Testosterone commonly prescribed to relieve symptoms in men who have low testosterone for no apparent reason other than aging
- The benefits and safety of this use have not been established even when symptoms are related to low testosterone
- Off label use of a controlled substance

Off label Testosterone Use

- FDA aware that testosterone prescribed to relieve symptoms in men who have low testosterone for no apparent reason other than aging *(off label----license risk!)*
- The benefits and safety of this use have not been established even when symptoms are related to low testosterone
- Increased risk of MI and stroke when "T" is used on label/off label

Labeling on Testosterone

- Possible increased risk of MI and stroke associated with testosterone use
- HCPs should make patients aware of risk when starting or continuing therapy with testosterone

What's Schedule IV mean?

- May lead to limited physical dependence or psychological dependence compared with Schedule III drugs

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

Schedule IV

Examples

- Benzodiazepines (alprazolam, clonazepam, diazepam)
- Temazepam (Restoril)
- Barbiturates (Long acting)
- Modafanil (Provigil)
- Midazolam (Versed)
- "Z drugs" (zolpidem, eszopiclone, and zaleplon)

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Non-Benzo Hypnotics

(aka: Z-drugs)

Benzodiazepine Receptor Agonists:

- FDA requires boxed warning for all of these meds
- Warnings about sleepwalking, driving, cooking eating without memory of these events
- Serious injuries, accidents, etc,

Non-Benzo Hypnotics

(aka: Z-drugs)

Benzodiazepine Receptor Agonists:

- **Start at low doses...especially for women and the elderly**
- **Beers List!!!**

What's Schedule V mean?

- **Lowest potential for abuse**
- **May lead to limited physical dependence or psychological dependence compared with Schedule IV drugs**

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

Schedule V

Examples

- **Anti-diarrheals**

Diphenoxylate + atropine (Lomotil)

- **Antitussives with codeine**
- **Pregabalin (Lyrica)**
- **Cannibidiol (Epidiolex)**

Practitioner's Manual – SECTION II, deadiversion.usdoj.gov

Lomotil

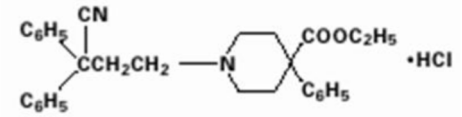
(diphenoxylate + atropine)

Diphenoxylate + atropine

- **2.5 mg diphenoxylate HCl**
- **.025 mg atropine sulfate**
- **Max is 20 mg daily**

Diphenoxylate

- **Diphenoxylate is a man-made narcotic chemically related to meperidine (Demerol)**

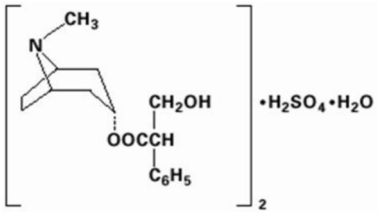


Diphenoxylate

- Diphenoxylate reduces diarrhea by prolongation of gastrointestinal transit time
- No pain-relieving action but in high doses can cause euphoria and physical dependence
- Approved by FDA in 1960!
- Not for use under age 13 years

Diphenoxylate + atropine

.025 mg Atropine



Why do we add atropine?

- To prevent abuse of diphenoxylate (discourages deliberate overdose)
- If Lomotil is taken in greater than recommended doses ➔ side effects from too much atropine will occur

Atropinism

- Atropinism (hyperthermia, tachycardia, urinary retention, flushing, dryness of the skin and mucous membranes)

Symptoms of Lomotil Overdose

Opioid and/or Anticholinergic Toxicity

- Respiratory depression
- Coma
- Delirium
- Incoherent speech
- Dryness of skin and mucus membranes
- Mydriasis
- Miosis
- Flushing
- Hyperthermia
- Tachycardia
- Hypotonia
- Tachypnea
- Seizures

Treatment of Lomotil Overdose

- Use a narcotic antagonist! (naloxone hydrochloride) for treatment of respiratory depression

Loperamide (Imodium AD)

- Binds to the gut wall opioid receptors

Loperamide
Mechanism of Action

- Slows stool transit in the intestine
- Reduces the number of bowel movements

Loperamide
Potential for Abuse

- Self-treat opioid withdrawal symptoms
- Euphoric effects with large doses

QUIZ

What's the maximum daily dose of loperamide?

Abuse of Loperamide

Doses: 70mg - 100mg per

- To prevent opioid withdrawal
- For opioid-related euphoric effects

More Examples of Abuse…

- Some abusers *add cimetidine, omeprazole, quinine* to boost the euphoric effects
- Intentionally consume high doses of loperamide ==> euphoria

Physical S/S of Abuse

Cardiac events

- QT prolongation, Torsades de Pointes, ventricular arrhythmias, syncope and cardiac arrest

Neurologic events

- Syncope

Respiratory

- Depression
- Arrest

Treatment of Loperamide Overdose

Cardiac Symptoms

- Torsades may not respond to magnesium sulfate
- Cardiac pacing, cardioversion may be needed

Treatment of Loperamide Overdose

Respiratory Symptoms:

- Use a narcotic antagonist! (naloxone hydrochloride) (anecdotal evidence)
- ***Loperamide's half-life is prolonged with gross overdosing, *naloxone could wear off* long before loperamide concentrations abate to a safe level

FDA to Limit Loperamide

- OTC packages limited through either use of blister packs or other single-dose packaging

DEA Registration

How do I get registered?

To Get Registered:

- DEAdiversion.usdoj.gov
- 1-800-882-9539 (Call Center)
- New Application or Renewal: Appendix H
- Renewed every 3 years
- If you choose to terminate, must notify DEA in writing

Practitioner's Manual – SECTION III, deadiversion.usdoj.gov

How much does 3 year registration cost for a "mid-level provider"?

a. $300
b. $400
c. $500
d. $731

Once DEA Registered:

"it must be maintained and readily retrievable and kept available for official inspection"

Practitioner's Manual – SECTION III, deadiversion.usdoj.gov

Recommendations from DEA

Practitioner's Manual – SECTION III, deadiversion.usdoj.gov

Recommendations from DEA

Keep blank Rx pads in a safe place where they cannot be stolen!

Practitioner's Manual – SECTION III, deadiversion.usdoj.gov

Quiz

Quiz questions not in handout

Mrs. Thibodeaux

Mrs. Thibodeaux received a prescription from you for alprazolam for acute anxiety. She comes today for a follow up and states that alprazolam made her "crazy for a whole day and she'll never take another one." She hands you her bottle of alprazolam.

What should you do?

Options for Disposal

If unused, unwanted, out of date, samples, must transfer them to a

Reverse Distributor:

someone who is authorized to receive such materials.

Practitioner's Manual – SECTION IV, deadiversion.usdoj.gov

Suppose there are no nearby locations……

Can the patient flush meds down the toilet?

Practitioner's Manual – SECTION IV, deadiversion.usdoj.gov

Proper Disposal of Meds

Do NOT: Flush expired or unwanted prescription or OTC drugs down toilet or drain unless the label or accompanying patient information specifically instructs you to do so.

Archve.EPA.gov, Aceessed June 9, 2019.

Options for Disposal

DO: Return unwanted or expired prescription or OTC meds to a drug take back program. Call your city or county government's household trash and recycling service and ask if a drug take back program is available in your community.

DEA: 1-800-882-9539 (for an authorized collector)

Archve.EPA.gov, Aceessed June 9, 2019;fda.gov

How do you dispose of Controlled Substances after a patient dies?

https://apps2.deadiversion.usdoj.gov/pubdispsearch/spring/main;jsessionid=s1g64qe_4BQA7lTjq0QOhi-D4oTkfc67fX-5g75b.web1?execution=e1s1

Household Disposal

1. **Take Rx drugs out of original containers**

Archve.EPA.gov, Accessed June 9, 2019.

Household Disposal

2. Mix drugs with an undesirable substance, cat litter, coffee grounds ***(makes less appealing to children or pets)***

Archve.EPA.gov, Accessed June 9, 2019.

Household Disposal

3. Put the mixture into a disposable container with a lid (butter tub or sealable bag) ***(makes them unrecognizable to people who intentionally go through trash to seek drugs)***

Archve.EPA.gov, Accessed June 9, 2019.

Household Disposal

4. Conceal or remove any personal info, Rx number, etc from the med container.
(protects your privacy and personal health info)

Archve.EPA.gov, Accessed June 9, 2019.

Household Disposal

5. Place sealed container with drug mixture, empty drug containers in trash. ***(prevents leakage)***

Archve.EPA.gov, Accessed June 9, 2019.

National Prescription Drug Take Back Day

April 19, 2019, 10:00 am to 2:00 pm

States have additional (often every 6 months) "take back" events.

Drug Disposal Information: deadiversion.usdoj.gov, Accessed June 16, 2019

Summary of Options to Dispose of Meds

1. **Find a reverse distributor**
2. **Dispose of by mixing with undesirable substance (per FDA)**
3. **Take Back Day**

Drug Disposal Information: deadiversion.usdoj.gov, Accessed June 16, 2019

What constitutes a Valid Controlled Substance Prescription?

Requirements:

- **Drug name**
- **Strength**
- **Dosage form**
- **Quantity prescribed**
- **Directions for use**
- **Number of refills (if any) authorized**
- **Name/address of pt, prescriber's name/address, and DEA number**

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Can a prescription for hydrocodone be written today and dated next month?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Can a prescription for a non-narcotic Schedule II (for ADD) be written today (initial Rx) with a second Rx dated 30 days later (for patient convenience)?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

12 year old "John"

John has been diagnosed with ADHD since age 8. He has responded well to dextroamphetamine/amphetamine (Adderall). He has complied with all of your requests to insure safety/efficacy with his medication. His mother asks if he has to come in monthly to "be checked" and receive another prescription.

Thoughts???

Issuance of Multiple Rxs for Sched II Substances

a. Each separate Rx is issued for legitimate medical purpose by an individual practitioner acting in the usual course of professional practice.

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Issuance of Multiple Rxs for Sched II Substances

b. The practitioner provides written instructions on each prescription…indicating the earliest date on which a pharmacy may fill each prescription.

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Issuance of Multiple Rxs for Sched II Substances

c. The individual practitioner concludes that providing the patient with multiple Rxs in this manner does not create an undue risk of diversion or abuse.

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Issuance of Multiple Rxs for Sched II Substances

d. The issuance of multiple Rxs is permissible under applicable state laws.

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Issuance of Multiple Rxs for Sched II Substances

e. The individual practitioner complies fully with all other requirements under the Controlled Subs Act and Code of Federal Regulations, as well as any applicable state laws.

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Can a prescription for hydrocodone be written by a nurse in the office and, then signed by the prescriber?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Can a prescription for hydrocodone be stamped with the prescriber's signature?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Can a prescription for hydrocodone be "called in" to a pharmacist under ordinary circumstances?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

A prescription for hydrocodone or another Schedule II medication may be "called in" (verbal order) to a pharmacist *in an emergency.* What's an example of an emergency?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Are you allowed to write a refill for a Schedule II medication?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Are you allowed to write a refill for a Schedule III-V medication?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

How many times may a Schedule III-V medication be refilled?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Can a prescription for alprazolam be "called in" to a pharmacist under ordinary circumstances?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Do you need a separate DEA registration for each clinic where you work---- in order to legally issue a prescription for a controlled substance?

Practitioner's Manual – SECTION V, deadiversion.usdoj.gov

Can a controlled substance be prescribed electronically?

Yes, the rule was established March 31, 2010, became effective June 1, 2010.
But, there are several requirements before this can happen.

Electronic prescriptions for controlled substances (EPCS), deadiversion.usdoj.gov

Requirements for Controlled Substances to be Prescribed Electronically

- Prescriber must complete application (and complies with requirements)
- Pharmacy must complete application (and complies with requirements)
- An auditor or certification body will issue a report stating provider compliance
- Provider has to send to pharmacy

Electronic prescriptions for controlled substances (EPCS), deadiversion.usdoj.gov

If EHR will allow prescriber to print but not send….

Or if the prescriber does have an approved/completed application

- Then, it is acceptable for prescriber to manually sign the prescription

Electronic prescriptions for controlled substances (EPCS), deadiversion.usdoj.gov

What OTHER Requirements for electronic prescription of controlled subs?

Identity Proofing, Need 2 forms:

a. Something you know (knowledge factor),
b. Something you have (a hard token stored separately from the computer being accessed), and
c. Something you are (biometric information)

Electronic prescriptions for controlled substances (EPCS), deadiversion.usdoj.gov

Become familiar with this language:

- A prescription for a controlled substance must be "in accordance with a standard of medical practice generally recognized and accepted in the United States"
- "…acceptable medical practice"

Become familiar with this language:

An example:

- Prescribing lortab for sleep

Become familiar with this language:

An example:

- Lortab has an indication for pain, not insomnia

Become familiar with this language:

- "…legitimate medical purpose in the usual course of professional practice"
- DEA says it is difficult to define this, so they've given examples of what's it's not

Become familiar with this language:

Examples:

- An inordinately large quantity or large numbers of prescriptions issued… compared to other prescribers

Become familiar with this language:

Examples:

- No physical exam was performed

Become familiar with this language:

Examples:

- No logical relationship between drugs prescribed and treatment allegedly existing

Where do I get more information?

- www.DEAdiversion.usdoj.gov

Part 2
Let's Talk about Opioids

Part 2-Opioids

- History
- How they work
- Patient Safety (Screening)
- Drug Drug Interactions with Opioids
- Side effects
- Alternatives to Opioids

Poppy Seeds

- Opium (exudate) is extracted from poppy seeds (Paper somniforum) in 1600s
- Used for thousands of years to produce:
  - Euphoria
  - Analgesia
  - Sedation
  - Relief from diarrhea
  - Cough suppression

Poppy Seed Extract

- Used medicinally to treat many maladies
- Used recreationally from early Greek and Roman times

Opium *plus* Alcohol

Laudanum ("something to be praised" in Latin)

- Called "Mental floss"
- Tincture of opium (10 percent powdered opium in an alcohol base)
- Used as a pain reliever and to heal various other conditions

Then……..early 1800s

- Morphine was isolated from opium to treat severe pain

Mid 1800s

- Hypodermic needle invented in 1856
- Drug abusers could then self administer opioids by injection

History and Background

Euphoria, tolerance and physiological dependence makes control of opioids DIFFICULT!

Terminology

- "Opium" is a Greek word meaning "juice," or the exudate from the poppy
- "Opiate" is a drug extracted from the exudate of the poppy
- "Opioid" is a natural or synthetic drug that binds to opioid receptors producing agonist effects

Quiz

What substance is responsible for a runner's "high" (if you believe that it exists)?

2 Natural Opioids

- Endogenous endorphins
- Juice of the opium poppy (morphine and codeine)

All Other Opioids

- Synthetic (like fentanyl, methadone) tramadol
- Semi-synthetic prepared from morphine (oxycodone, hydrocodone, hydromorphone, and oxymorphone)

Why do we prescribe Opioids?

Oral Opioids

- Moderate to severe pain
- Dental pain, post op pain, pain due to trauma

Fact

Acute use of opioids turns into chronic use in 50% of patients.

Clinical Resource, Analgesics for Acute Pain. Pharmacist's Letter/Prescriber's Letter. May 2018.

What are the Goals of Opioid Therapy?

- Improve and/or stabilize pain intensity: reduction of 30% is considered a win!
- Improve function: I want to be able to work, I want to be able to go shopping with my daughter, I want to be able to take my grandson fishing
- Improve quality of life

How do Opioids Work?

- Morphine
- Codeine
- Hydrocodone
- Others

3 Opioid (Endorphine) Receptors

- *Mu* (μ1 and μ2)
- *Kappa* (modest anesthesia effect; little or no respiratory depression or dependence)
- *Delta* (don't know what it does)

3 Opioid (Endorphin) Receptors

- ***Mu*** **(μ1 and μ2)**
  - **Mu1 is located outside spinal cord; responsible for pain interpretation**
  - **Mu2 is located throughout CNS**
- ***Kappa*** **(K 1, K2, K3) modest anesthesia effect; little or no respiratory depression or dependence)**
- ***Delta*** **(1, 2) might help regulate mu activity)**

Activation of Receptor Sites

Response	Mu1	Mu2	kappa
Analgesia			modest
Respiratory Depression			
Euphoria			
Dysphoria			
Constipation			
Dependence			

No New Drugs

Old drugs in new delivery systems

- **Morphine**
- **Methadone**
- **Hydrocodone**
- **Oxymorphone**
- **Oxycodone**
- **Buprenorphine**
- **Fentanyl**
- **Hydromorphone**
- **Tapentadol**

Table 2. Classes of Opioids

Phenanthrene Opioids	Nonphenanthrene Opioids
Codeine	Piperidine derivatives:
Hydrocodone	Fentanyl
Hydromorphone	Meperidine
Morphine	Sufentanil
Oxycodone	Other:
Oxymorphone	Buprenorphine
	Methadone
	Tramadol

Source: References 11, 14.

USpharmacist.com

No New Drugs

- **Old drugs in new delivery systems**
- **All scheduled drugs**
- **High potential for abuse**
- **Diversion does occur**

Table 2. Classes of Opioids

Phenanthrene Opioids	Nonphenanthrene Opioids
Codeine	Piperidine derivatives:
Hydrocodone	Fentanyl
Hydromorphone	Meperidine
Morphine	Sufentanil
Oxycodone	Other:
Oxymorphone	Buprenorphine
	Methadone
	Tramadol

Source: References 11, 14.

Patient Safety

Patient Screening

Quiz

Any opioid can cause death or serious side effects, but risks are greater with extended release (ER) or long acting (LA) opioids

WHY?

www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.htm

Screen patients for risks *before* prescribing Opioids

1. Overdose
2. Abuse by patient

Patient Safety: Overdose

- Unintentional overdose is common
- 90% of OD is unintentional
- Respiratory Depression/Death are possible

Who is at High Risk for Opioid Emergency?

- Patients who take 50 mg/day or more of oral morphine equivalents
- Those who take long-acting opioids
- Switching opioids
- CNS depressants (EtOH, benzos, etc.)
- COPD, sleep apnea, etc.

What can be done to keep patients safe?

Need a HOME PLAN!

- Most opioid emergencies occur in the home
- Most are witnessed by close friends, family

What can be done to keep patients safe?

Need a HOME PLAN!

- FDA has approved 2 products that reverse opioid overdose that can be administered at home

What can be done to keep patients safe?

- Naloxone nasal spray: Narcan ($125)
- Naloxone auto-injector (Evzio up to $3750)
- Naloxone Kit (about $50): pharmacist puts kit together

Naloxone

Nalaxone nasal spray: Narcan ($125)

- Does not need to be inhaled to work
- Lie patient on his back
- Tilt patient's head back gently and the tip of the nozzle inserted into the patient's nostril until the fingers holding the nozzle are on either side of the person's nose
- Remove from nostril
- Call 911

Naloxone

Nalaxone auto-injector (Evzio up to $3750)

- "talks" user through the injection
- Place injector against the outer thigh (can inject through pants)
- Press the injector firmly and hold for 5 seconds (injector makes a hiss and click sound during injection)
- Call 911

Naloxone Kit

Rx 2 naloxone doses: for IM

- Naloxone 0.4mg/ml plus 2 syringes
- Use shoulder, thigh or upper buttocks
- Inject at 90 degree angle

Rx 2 naloxone doses: for Intranasal

- 2mg/2mL prefilled syringes and 2 atomizers (mucosal atomizer device (MAD 300)
- Give short vigorous push delivering half naloxone into each nostril

Prescribers Letter; Detail Document #320122

What else can be done? Keeping Patients Safe

- Call 911 EVEN IF NALOXONE administered and patient wakes up!
- Naloxone lasts about 30-90 minutes, symptoms can return when it has been metabolized

After Naloxone Administration

- Position patient on his side: they vomit!
- May repeat dose every 2-3 minutes if remains unresponsive or no spontaneous breathing
- Patient may experience opioid withdrawal symptoms: fever, agitation, combativeness, sneezing, yawning, runny nose (none are usually life-threatening)

Quiz

What happens if naloxone is given to someone who is unconscious and it is NOT due to opioid OD?

Substance Abuse and Mental Health Services Administration. SAMHSA opioid overdose prevention toolkit. HHS publication no (SMA) 16-4742. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2016. http://store.samhsa.gov/shin/content//SMA14-4742/Overdose_Toolkit.pdf (Accessed July 18, 2019).

Take Home Point

- Universal precautionary approach
- Prescribe naloxone with EVERY opioid prescription (not just high risk patients)

Screen patients for risks *before* prescribing Opioids

1. Overdose
2. Abuse by patient

"John"

- John is a 45 year old male smoker who has hypertension, type 2 diabetes. His BMI is 35, he doesn't exercise.
- Does it seem prudent to screen him for hyperlipidemia?

By Analogy….

If you take opioids, we must screen you for other risks!

Patient Assessment

Risk Factors for Prescription Drug Abuse

Number 1 Risk Factor for Abuse:

- Ask about history of drug abuse
- Get good medical history from patient

What else must you assess for?

Risk Factors for Prescription Drug Abuse

Number 2 Risk Factor:

- Psychiatric co-morbids: bipolar, anxiety, depression
- Must screen for these!
- Get good medical history from patient

What else needs to be done before prescribing opioid?

- Helps to ensure that patients and caregivers understand goals, risks, and safe medication use
- Can include commitments for follow up visits, monitoring for compliance

www.fda.gov FDA Blueprint

Drug-Drug Interactions and Opioids

It's about Patient Safety!

- You may legally prescribe most/all of the meds we are about to discuss
- You may have patients who take these meds
- It is easy for patients to get into trouble with opioids; especially combos of meds

Opioid Analgesics

41% of all fatal overdoses involve opioid analgesics:

- Benzos involved 31%
- EtOH 19%
- Highest overdose rates are in middle aged adults; Whites, American Indians, Alaska natives
- Deaths: Males > Females

www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.htm

Drug Drug Interactions (DDIs)

- 5 or more drugs increase the risk of DDI
- Pharmacodynamic (PD) Interactions
- Pharmacokinetic (PK) Interactions: Effect absorption, metabolism, distribution, excretion
- These interactions could increase or decrease effect of drug

CNS Depressants Plus Opioids

- *Sedatives:* EtOH
- Hypnotics: Pot
- *TCAs:* phenothiazines (thorazine, prolixin, compazine)
- Respiratory Depression
- Hypotension
- Sedation
- Coma

Alcohol plus Opioid

- Magnifies the effect of the opioid
- "Dose Dump": EtOH can impair the delivery system of the long acting opioid
- Example: Palodone plus EtOH: marked increase release of opioid….now pulled off the market

Alcohol plus Opioid

- All new opioid delivery systems must be studied for effect with alcohol ("dose dump")
- Teach patient: NO EtOH with opioids!!!

Skeletal Muscle Relaxants Plus Opioids

- Increase risk of respiratory depression
- Enhance neuromuscular blocking action

blog.ng.jovago.com

MAO Plus Opioids

(Mostly used for Depression, but some are used for bulimia)

- May precipitate serotonin syndrome
- Agitation, coma, death
- Many bizarre symptoms associated with serotonin syndrome
- Examples: selegiline transdermal (Emsam), isocarboxazid (Marplan), phenelzine (Nardil), tranylcypromine (Parnate)

Anticholinergics Plus Opioids

- Effect magnified by opioids
- Urinary retention
- Constipation

Anticholinergic Medications

Anti-cholinergic Side Effects

Memory impairment, confusion, hallucinations, dry mouth, blurred vision, urinary retention, constipation, tachycardia, acute angle glaucoma

Quiz: What do these drugs all have in common?

- Macrolides, quinolones, telithromycin, sulfonamides
- Amitriptyline, citalopram, paroxetine, sertraline, venlafaxine, fluoxetine
- Albuterol, levalbuterol, salmeterol
- Phenylephrine, pseudoephedrine
- Cocaine

QT interval Prolongation with Opioids

- Methadone: 3-5% of prescriptions for analgesics; causes 30-50% of the ODs
- Buprenorphine

How to Handle:

- Serial EKGs
- Consider alternatives in patients who are on other meds that prolong QT intervals

CYP 450 Enzymes

- 3A4 Enzymes: responsible for 50% of meds that are metabolized
- 2D6 involved in metabolism of many pain meds

Codeine => morphine
Hydrocodone=> hydromorphone
Oxycodone=> oxymorphone
Morphine=> hydromorphone (trace metabolite)

CYP 450 Enzymes

- *3A4 Enzymes*: responsible for 50% of meds that are metabolized
- Many drugs are 3A4 inhibitors: statins, CCBs, benzos, warfarin, Beta blockers, antifungals
- It turns OFF active drugs! If these are inhibited, then amount of drug is GREATLY MAGNIFIED!!!

The Opposite Can Happen!

- If a medication is a Prodrug, a 2D6 inhibitor can decrease the effects of the drug
- Codeine is a Prodrug
- This is the opposite of what happened in the previous slide where 3A4 caused an increase in drug levels
- Inhibition with a prodrug can DECREASE drug levels!

CYP 450 Enzymes

- If you inhibit an active drug, you MAGNIFY the effects of the drug!
- If you inhibit a ProDrug, you DECREASE the effect of the drug!

Codeine => morphine

Codeine is a prodrug…..decreased effect of med

CYP 450 Influence

Medication	CYP 450
Tramadol	3A4, 2D6
Codeine	2D6
Hydrocodone	3A4
Oxycodone	2D6, 3A4
Acetaminophen	2D6
Fentanyl	3A4
Methadone	3A4, 2D6, 2B6, 2C9, 2C19

Which medication has the greatest potential to cause a DDI?

CYP 450 Enzymes

4 opioids do NOT go thru the CYP 450 System (MOTH)

- **Morphine**
- **Oxymorphone**
- **Tapentadol (Nucynta, Nucynta ER)**
- **Hydromorphone**

P-glycoprotein (PGP)

- **Drug Transporter across cell membranes**
- **Limits absorption, distribution of many drugs (important in preventing toxicity)**
- **Responsible for concentrations of drugs in cells and in the serum**
- **Drugs that inhibit the PGP system can causes changes in concentrations of drugs that use this system**

P-glycoprotein (PGP)

Examples of PGP drugs:

- **Morphine**
- **CCBs**
- **Cyclosporin**
- **Digoxin**
- **Macrolide antibiotics**
- **Protease inhibitors**
- **Quinidine**
- **Dabigatran**

Australian Prescriber.com

PGP Inhibitor

- **Would increase the concentration of morphine**
- **Examples: quinidine, digoxin, verapamil, ketoconazole, loperamide, azithromycin, others**

QT Prolongation

- **Long QT Syndrome (LQTS)**
- **Increased risk of ventricular tachycardia**

Quinolones and macrolides can prolong QT intervals.

Take Home Point

Beware of drug-drug interactions with opioids!!!

Patient Assessment *During* Opioid Use

Patient Assessment and Monitoring

1. Adverse Effects: Nuisance
2. Adverse Effects: Serious

Common Adverse Effects: Nuisance

- Sedation: goes away over time
- Constipation: does not go away over time!

Constipation

- Opioids slow down motility in the gut
- Constipation is a common side effect
- OIC: Opioid induced constipation

OIC

Table 1. Commonly Used Definition of Opioid-Induced Constipation
Diagnosis of Opioid-Induced Constipation
1. Fewer than 3 bowel movements per week
2. Hard or lumpy stools
3. Sensation of incomplete evacuation
4. Sensation of anorectal obstruction
5. Straining with defecation
6. Bloating and abdominal pain relieved with bowel movements
7. Small stools
8. GERD (potentially)

GERD, gastroesophageal reflux disease
Based on references 11 and 17.

www.practicalpainmanagement.com

Approach to Management of Opioid Induced Constipation

- Consider a bowel regimen when opioid is initiated
- Lifestyle changes: fluids, fiber, prunes, physical activity
- Consider osmotic laxative (polyethylene glycol) (Miralax)
- Cheap, well tolerated, safe long-term and it works!

Prescriber's Letter: June 2015; Vol: 22

Opioid Induced Constipation: Plan B

- Consider a stimulant laxative (bisacodyl)
- No proof that this produces laxative dependence

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Opioid Induced Constipation: Plan C

- Consider an opioid antagonist: Mechanism of Action: Inhibit opioid binding in the gut
- Do not inhibit analgesia

Opioid Induced Constipation: Plan C

- Consider an opioid antagonist: Naloxegol (Movantik), methylnaltrexone (Relistor)

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Why are Opioid Antagonists Plan C?

- Expensive!
- Naloxegol ($10/day)
- Methylnaltrexone ($72/day) by injection
- STOP laxatives!

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Opioid Induced Constipation WHAT DOES NOT WORK!

- Stool softeners don't produce motility
- "All mush and no push"! ☺

Prescriber's Letter: June 2015; Vol: 22

Other Common Adverse Effects

- Itching
- Edema and sweating
- Dizziness
- Confusion

"Other" Types of Reactions are Pretty Common

Pseudoallergic Reactions

- Don't be fooled by the name!!!!!
- Range from mild to fatal
- Uncertain how these reactions occur
- Probably mast cell degranulation by a non-IgE mediated mechanism
- ***Don't worsen with repeated exposure***

Example 1: Opiates

Pseudoallergic Reactions

- Opiate analgesics: Morphine and codeine cause direct mast cell activation

Common Culprits

Pseudoallergic Reactions

- Radiocontrast medium
- *Opiates*
- NSAIDs
- Muscle relaxants (atracurium, vecuronium, succinylcholine, curare)
- Chemo agents
- Vancomycin: "Red man" syndrome

How to manage Adverse Effects

- Treat with another drug: drug cascade
- Rotate opioids
- Dial down the dose of opioid

www.medicalnewstoday.com

Adverse Effects: Serious

- Respiratory depression
- Death

Umanitoba.com

Risk Factors for Respiratory Depression

1. **Initial dose is too high!**
   - ✓**Start low and go slow!**

2. **Must know whether your patient is opioid naïve or opioid tolerant**
   - ✓**NEVER prescribe a LA or ER opioid to a patient who is opioid naïve….you'll probably kill them!**

Risk Factors for Respiratory Depression

- **Opioid plus benzodiazepine**
- **Opioid plus EtOH**
- **Opioid plus benzo plus EtOH (most lethal combo)**
- **Opioid plus diphenhydramine**
- **Opioid plus "Z-drugs"**

Patient Scenario

- **Patient not feeling well during cough and cold season. Goes to bed early and takes prescribed meds plus Benadryl:**
- **LA opioid**
- **SA opioid**
- **Trazodone**
- **Benadryl**

Other Risk Factors for Respiratory Depression

- **Sleep apnea patient**
- **COPD/Asthma patient**
- **Smoking: produces some degree of respiratory impairment**
- **Heart failure patient**
- **Obesity**
- **Others?**

Avoidance of Respiratory Depression

- **Patient Education**
- **Family Education**
- **Informed providers**
- **Nalaxone (Narcan) Autoinjector**

It's all about patient safety!

Opioid Alternatives?

Non-Opioid Analgesics

Terms

- **Acute Pain – Pain that usually starts suddenly and has a known cause, like an injury or surgery. It gets better and lasts less than three months**
- **Chronic Pain – Pain that lasts 3 months or more and can be caused by a disease or condition, injury, medical treatment, inflammation, or unknown reason**

Urgent Care Clinic

A 24 year old male was in bicycle accident about an hour ago. He has a non-displaced fracture of the head of the humerus. He has abrasions on his elbow, arm, and lateral leg. His arm pain is 5-6/10.

What medication class do you usually consider first?

Preferred Analgesics for Pain

Always consider a non-opioid first!

Is an NSAID appropriate for his pain?

NSAID

- **One in 2-3 patients with moderate to severe pain report 50% reduction in pain over 4-6 hours**
- **Don't forget about ice!**

NSAIDs: Oral, Parenteral

- Use in mild to moderate pain
- Abdominal, dental surgery
- Musculoskeletal injury
- DO NOT USE for CABG post-op!

Urgent Care Clinic

A 24 year old male was in bicycle accident about an hour ago. He has a non-displaced fracture of the head of the humerus. He has abrasions on his elbow, arm, and lateral leg. His arm pain is 5-6/10.

Which 2 NSAIDs are most appropriate to treat his pain? Why?

a. Naproxen
b. Ibuprofen
c. Celecoxib
d. Meloxicam

How much Ibuprofen?

- 400 mg about as effective as 800 mg
- 200-400 mg produces analgesia
- Higher doses used to reduce inflammation

NSAID plus Acetaminophen

- Better efficacy if used WITH acetaminophen
- Acetaminophen 500-1000 mg plus ibuprofen 200-400 mg every 6 hours PRN

What about an injectable NSAID?

Injectable NSAIDs

- Examples: Diclofenac, Ibuprofen, Ketorolac injectable
- Injectable ketorolac equally effective vs oral ibuprofen for moderate to severe pain

Speaking of Ketorolac…

- Oral ketorolac similar efficacy to other NSAIDs but risks > benefits

Urgent Care Clinic

A 84 year old female slipped in the grocery store about an hour ago. She has a fractured nose and moderate facial swelling. Her face pain is 5-6/10. She has GFR 48.

What medication class do you usually consider first?

What could be considered to treat her pain?

a. Naproxen
b. Ibuprofen
c. Acetaminophen
d. Hydrocodone

Acetaminophen

- Oral, rectal, IV
- Use when NSAID is inappropriate (or consider first)
- One in 3 to 4 patients with moderate to severe pain has a 50% reduction in pain over 4-6 hours with 1000 mg acetaminophen

How much acetaminophen?

Acetaminophen

- One in 3 to 4 patients with moderate to severe pain has a 50% reduction in pain over 4-6 hours with 1000 mg acetaminophen
- 1000 mg NOT more effective at reducing pain than 500 mg
- In liver impairment limit dose to 2-3 grams instead of 4 grams daily

IV Acetaminophen ($$$$$)

- Use if patient is unable to take by mouth or rectally
- No superior efficacy vs oral or rectal
- $160/day vs .10/day (oral)

Take Home Point: Consider a non-opioid FIRST!

Thank you!

For questions or to contact me:

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