THE PRESCRIPTION OPIATE EPIDEMIC

Opiates: A Pharmacist's Opportunity to Educate

Objectives

- At the end of this presentation one should be able to:
  - Recognize and identify different types of opioids, side effects, dosages.
  - Identify the mechanism of action, overdose risks and treatments.
  - Understand regulations, opioid abuse and its impact on healthcare costs.
  - Achieve better clinical outcomes while decreasing potentials for abuse.

Terminology

- Opium
  - A mixture of alkaloids from the poppy seed
- Opioids
  - All compounds that bind to opiate receptors
- Opiates
  - Describes those opioids that are alkaloids derived from opium poppy seed
    - Includes morphine and codeine

History

- In 1803, Friedrich Sertürner (Germany)
  - Morphine extracted from opium
  - "Father" of Morphine
- Dr. Charles Wood
  - Scottish physician
  - invented hyperdermic needle
- Dr. Edward Livenstein
  - German Physician
  - 1st to accurately and comprehensively describe addiction

Heroin

- Chemical Name
  - Diacetylmorphine
    - Synthesized and briefly promoted as more effective and less addictive than morphine
    - In early 20th century,
      - legally marketed in pill form
      - changed ways opioids were used for treatment of pain and addiction
        National and International organizations
        First to control use, addiction, Opioid Maintenance Therapy (OMT)
    - OMT
      - Drugs used morphine to methadone

National Statistics

- National Survey on Drug Use and Health
  - Reported the number of first time abusers of prescription(RX) opioids increased from 628,000 in 1990 to 2.4 million in 2004
  - ER visits increased 45% from 1997-2002

National Statistics

- Overview of Drug Overdose
- Occurs in 14-35% of people > 20 years old
  - One-third National Population
  - 12-34% patients treated with opioids will abuse the medicines
  - Every 19 minutes someone dies from opioid abuse

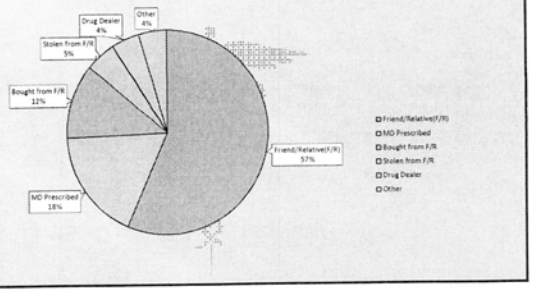
National Statistics

- Between 2000-2014
  - Deaths from drug overdose totaled nearly a half-million
    - August, 2014, 41,300 drug overdoses occurred*
  - CDC reported rate of opioid overdose has tripled
  - Increase use of opioids for legitimate medical purposes is accompanied by increase in prevalence of nonmedical use of prescription(RX) opioids
    - In 2004, 198,144 users
    - In 2009, 477,936 users
      - Fastest growing rate 140% increase

National Statistics

- Three- fourths of 41,300 Drug Overdoses
  - 23,000 pharmaceutical overdose
  - 18, 500 illegal drugs
- 17,000 deaths due to Opioids
- 72.2% Abused opioids were obtained via friend or relative

How Opioids Were Obtained



Opioid Categories

- Semi-synthetic Opiates
  - Synthesized drugs from naturally occurring opiates
    - Heroin from morphine
    - Oxycodone from thebaine
- Synthetic Opioids
  - Methadone
  - Fentanyl
  - Propoxyphene

Mechanism of Action

- Mechanism of Action
  - Opioids act by binding to specific proteins called opioid receptors
  - Primary receptor
    - Mu

Mechanism of Action

- Mu Receptors
  - Responsible for supraspinal analgesia, respiratory depression, euphoria, sedation, decreased GI motility, pruritus, anorexia, and physical dependence
  - Opioid receptors widely distributed
  - Pain modulation situated in CNS/PNS
  - Bind to endogenous opioid peptides (endorphins)
    - Pain modulation and numerous other functions in the body
    - Mediated in deep structures of brain
  - Other receptors
    - Kappa and Delta

Mechanism of Action

- Functions
  - Modulation of reinforcement and reward mechanism, mood and stress
  - Powerful reinforcement which leads to cravings
  - Positive mood effects
    - euphoragenic or pleasurable effects

Dosage Forms

- Routes of Administration
  - Oral
  - Transdermal
  - Intravenously
  - Oral/Transdermal
    - Usually given in ambulatory setting

Methods of Abuse

- Oral Administration Variants
  - Without Tampering
    - Product ingested intact but taking more than prescribed
  - Tampering
    - Crushing, cutting, grating, liquidizing and vaporizing
- Non-oral Administration Variants
  - Inhalation (snorting)
  - Injection
  - Smoking

Drug Products

- Combinations
  - Hydrocodone/acetaminophen(APAP)
    - Vicodin, Lorcet, Lortab, Norco
  - Hydrocodone/ibuprofen
    - Vicoprofen
  - Tramadol/APAP
    - Ultracet
  - Oxycodone/APAP
    - Endocet, Roxicet, Percocet
  - Oxycodone/aspirin(ASA)
    - Percodan
  - Codeine/APAP and Codeine/ASA

Labeling Change

- FDA in 2013
  - Warning use of codeine products regarding overdose deaths in children after tonsillectomy
  - Children of certain ethnic groups ultra-rapid metabolizes codeine
    - Increase serum concentration of morphine
    - use extreme *caution* or no *codeine* for *children*
  - Long acting opioid and extended release opioid labels changed
    - should only be used for severe pain which require 24 hr./day, long term treatment, and when alternative options are inadequate

Drug Products

- Single entity
  - Morphine containing brands
    - Avinza, Kadian, MS Contin, MSIR, Astramorph
  - Oxycodone
    - OxyContin, Roxicodone, Oxecta
  - Fentanyl
    - Duragesic, Actiq, Fentora
  - Hydromorphone
    - Diluadid, Exalgo
- Oxymorphone
  - Opana

Drug Products

- Single entity
  - Methadone
    - Dolophine, Methadose
  - Meperidine
    - Demerol
- Quick List of Increasing Strength
  - Codeine
  - Hydrocodone
  - Morphine
  - Oxycodone
  - Hydromorphone
  - Fentanyl

Drug Products

- Parenteral Opioids
  - Most frequently used for acute pain
    - Morphine, hydromorphone, fentanyl
    - Neuraxial administration
      - Increasing as part of a multimodal acute management plan

Opioids

- Abuse
  - Both addiction and chronic pain have a multifactorial etiology
  - Opioids remain controversial due to side effects, long term efficacy function outcomes, potential for drug abuse
- Addiction
  - Hesitancy to prescribe opioids maybe related to perceived or real risks with regulatory legal scrutiny when prescribing controlled substance
  - Equal pressure exists for clinicians to address healthcare needs in these patients in addition to their addiction
- Defining the Patient
  - Tolerance
    - A decreased subjective and objective effect of the same amount of opioids used over time which concomitantly requires an increased amount of the drug to achieve the same effect

Definitions

- Physical dependence
  - A characteristic set of signs and symptoms that occur with the abrupt cessation of an opioid
  - Symptoms typically abate when an opioid is tapered under medical supervision
- Addiction
  - Chronic disease that represents an idiosyncratic adverse reaction in biologically and psychosocially vulnerable individuals
- Aberrant drug related behavior
  - May include the use of alternative routes of administration of oral formulations
  - Concurrent use of alcohol or other illicit drugs and
  - Repeated resistance to changes in therapy despite evidence of adverse effects

Identifying Aberrant Medication-Related Behavior

Portenoy and Payne's Aberrant Behavior

1. Selling prescription drugs
2. Forging prescriptions
3. Stealing drugs
4. Injecting oral formulations
5. Obtaining prescription drugs from nonmedical sources
6. Concurrently abusing alcohol/illicit substances
7. Escalating doses on multiple occasions despite warnings
8. *Losing* prescriptions on multiple occasions
9. Repeatedly seeking prescriptions from other providers/emergency departments/urgent care clinics without informing the provider or after warnings to desist
10. Evidence of deteriorating function as a result of drug use

Opioids Dosage

- Determining the dose
  - Patient either opioid naïve or tolerant
    - Tolerant
      - Taking regularly scheduled RX opioids(ops). or
      - History of substance abuse related to illicit drug use or
      - Participation in OMT
- Under dosing
  - Strategy is to continue a previously used ops. while treating the acute pain separately
  - Calculate a larger dose to treat acute pain that incorporates an equinanalgesic dose of previous ops.
  - Accurately and safely calculate equianalgesic opioid dose when converting from drug to drug

Opioid Potency Comparison

Medication	Route	Time to Effect	Duration	Routine Dosage Equivalent
Morphine Sulphate	IV	5-10 min	3-6 hours	10 mg IV
	IM	15-30 min	3-6 hours	10 mg IM
	PO	30-60 min	3-6 hours	30-60 mg PO
Oxycodone	PO	10-15 min	4-6 hours	10-20 mg PO
Hydrocodone	PO	30-60 min	4-6 hours	15-30 mg PO
Fentanyl	IV	Immediate	1-2 hours	50 micrograms IV
Hydromorphone	PO	15-30 min	4-6 hours	7.5 mg
	IV	15 min	4-6 hours	1.5 mg
	IM	15 min	4-6 hours	1.5 mg
Codeine	PO	30-60 min	4-6 hours	200 mg
Nalbuphine	IM	15 min	3-6 hours	10 mg

IV = intravenous; IM = intramuscular; PO = orally;
Routine dosage equivalent to Morphine 10 mg IM or IV
Medically reviewed by John A. Daller, MD; American Board of Surgery with subspecialty certification in surgical critical care

Clinicians Should Note

- Opioids should be used when benefits for pain and function are expected to outweigh risks
- When used, prescribe the lowest effective dosage
- Carefully reassess benefit and risk >50 morphine mg equivalent (MME)
- Avoid concurrent opioid and Benzodiazepine whenever possible
- Evaluate therapy every 3 months or more frequently
- Review PMDP data-avoid combo and high-risk therapies

Opioid Overdose Risks

- Situations that increase risks
  - Dispensing high dose opioids > 50 MME daily
    - titrate up to < 90 MME slowly if needed per individual patient
    - Examples of regimens > 50 MME
      - Methadone 10 mg. p.o. q 12 hrs. = 60 MME
      - Oxycodone 10 mg. p.o. q 6 hrs.
      - Hydrocodone 10mg p.o. q 4 hrs
      - Fentanyl 25 mcg patch q72 hrs
  - Duration of opioid use > 90 days
  - Overlapping opioid RX's
  - Using methadone for pain
  - Rotating from one opioid to another because of incomplete cross-tolerance

Steps for converting or rotating between opioids

- Calculate total mg dose taken in past 24-hours.
- Determine equianalgesic dose (Table 1)
- If pain is controlled on current opioid, reduce the new opioid daily dose by 25-50% to account for cross-tolerance, dosing ratio variation, and interpatient variability.
- If pain is uncontrolled on the current opioid, increase opioid daily dose by up to 100-125%.
- Titrate liberally and rapidly to analgesic effect during first 24 hours.
- Monitor for adverse events and effectiveness.
- Reassess the analgesic effect every 2-3 days.

Table 1. Opioid Equianalgesic Doses

Opioid Agonist	Parenteral Dose, mg (IV, SC, IM)	Oral Dose	PO:IV	Duration of Action, (hours)
Morphine	10 mg	30 mg	3:1	3-4
Morphine, long-acting (Avinza, Kadian)	-	30 mg	-	12
HYDROmorphone (Dilaudid)	1.5 mg	7.5 mg	5:1	2-3
OxyMorphone (OxecTA)	-	15-20 mg	-	3-5
Oxycodone, long-acting (OxyContin)	-	20 mg	-	12
HYDROcodone (Vicodin, Lortab)	-	30-45 mg	-	3-5
OxyMorphone (Opana)	1 mg	10 mg	10:1	3-6
Oxymorphone, long-acting (Opana ER)	-	10 mg	-	12
Codeine	-	180-200 mg	-	4
Fentanyl*	0.2 mg	-	-	2
Methadone**	-	-	-	-

*See Table 2 for fentanyl patch conversion
**Methadone dosing, always consult pain or palliative care specialist.

Transdermal Fentanyl

Conversion from morphine (or equivalent) to fentanyl transdermal:
- Calculate the total 24-hour morphine dose (or morphine-equivalent).
- Select microgram per hour dose of transdermal fentanyl based on Table 2.
- Decrease new dose 30-50% to allow for incomplete cross-tolerance.
- Manage breakthrough pain with morphine/short-acting opioid PRN.
- Titrate patch to effect every 72 hours.

Table 2. Conversion of Opioid Analgesics to Fentanyl Transdermal

Current Opioid Analgesic	Daily Dosage (mg/d)			
Morphine PO	60-134	135-224	225-314	315-404
Morphine IV/IM	10-22	23-37	38-52	53-67
Oxycodone PO	30-67	67.5-112	112.5-157	157.5-202
Oxycodone IV/IM	15-33	33.1-56	56.1-78	78.1-101
Codeine PO	150-447	448-747	748-1047	1048-1347
Hydromorphone PO	8-17	17.1-28	28.1-39	39.1-51
Hydromorphone IV	1.5-3.4	3.5-5.6	5.7-7.9	8-10
Meperidine IM	75-165	166-278	279-390	391-503
Methadone PO	20-44	45-74	75-104	105-134
Methadone IM	10-22	23-37	38-52	53-67
	Recommended fentanyl transdermal dose (q72h)			
Fentanyl transdermal (Duragesic)	25 mcg/h	50 mcg/h	75 mcg/h	100 mcg/h

Opioid Overdose Risks

- Concomitant opioid –alcohol use
- Additional Rx's for Benzodiazepine and other CNS depressants
- Person takes as directed, MD miscalculate dose
- Patient not taking as prescribed
- Patient misunderstood directions for use
- Communities where 1st responders (911) take longer than normal
- Any patient with known or suspected substance abuse
- Health conditions associated with increase overdose risks
  - Hepatic, pulmonary, renal dysfunction
  - Mental health condition
  - Previous Overdose, Bad reaction to opioid, Substance use disorder

Medications used to treat opioid addiction

- Suboxone, Subtex (Buprenorephine)
- Revia (naltrexone)
- Methadone

- Suboxone
  - Used for withdrawal/detoxing from opiate
  - FDA approved CIII
  - Partial mu agonist
  - Doesn't lead to a greater high with higher amount of drug
  - Decrease cravings, decrease withdrawal, blocks euphoric effects
  - Used to get people off more addictive drugs
    - Heroin or OxyContin
    - Tablets taken sublingually

Suboxone

- Side effects and dangers
  - Potentially addictive
  - Experience withdrawal symptoms as you come off
  - Increase drowsiness due to other drugs and alcohol
  - Overdose can cause slow breathing seizure, confusion, loss of consciousness, coma, death
  - Drug must be tapered

Methadone

- Synthetic mu agonist
- Evolved beyond traditional role in preventing opiod withdrawal of patients enrolled in Methadone Maintenance Programs
- Now used in management of severe pain with cancer or non-cancer related chronic pain
- Half-life of approximately 24 hrs
- Infusion helps prevent recurrence of respiratory depression
- Side effects
  - Causes airway relaxation which leads to airway obstruction and sleep apnea
  - Benzo's contribute to death by exacerbating the adverse effects of methadone
  - Patient history and clinical presentation are the best indicators of toxicity

Naloxone

- Pure opioid antagonist that competively bind Mu receptor only when an opioid present and bound
- Effective via IM, SC, SL or endotracheal tube, Intranasal or nebulization
- No tolerance or dependence associated with use
- Reversal of opioid toxicity is dose dependent. Increased drug potency leads to increased number of doses to reverse symptoms
- Has a greater affinity to bind receptor site thus decreases respiratory depression (partially or fully)
- Individual may experience rebound toxicity and /or acute respiratory depression due to short duration of action (30-90min.)
- Start with the smallest effective dose (0.04mg increase q 3 min.) until reverse
- 2014 FDA approved SC, IM for layperson
  - Minimum 2 dose kits

Naloxone

- Naloxone is now available for layperson use
  - Lack of providers
  - RX cost and lack of RX insurance
  - Expense of MD visits
- Side effects
  - Potentiating withdrawal symptom you see mild flu to severe agitation, hypertension(HTN) and return of pain
  - Severity of withdrawal is drug and dose dependent
  - Rare cases report seizures, arrhythmia, HTN reaction
  - Not effective in treatment of Non-opioid RX meds
    - Example: Benzo's or Barbiturates

Economics of Opioid Abuse

- Since the 1990's
  - 10X increase in use of opioids
  - Significant financial burden on healthcare system
    - Patients/Public
      - Time lost from work
      - Increased office visits
      - Doctor and RX's shopping
      - Rehabilitation facilities

Economics of Opioid Abuse

- Risk Evaluation and Mitigation Strategy (REMS)
  - >200 REMS programs approved by FDA between 2007-2014
  - Mandating prescriber and patient education to encourage proper patient screening and appropriate monitoring
  - Requires time and financial commitment
    - Approximately 3 hours M.D. education
- REMS
  - Goals
    - Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER and LA opioids
    - Manufacturers of ER/LA opioids and methadone required to provide prescriber education through accredited continuing education and information for patients on risks and benefits

REMS and Economic Impact

- Doctor Requirements
  - Knowledge of policies governing therapies both federal and state
  - Ongoing management of opioids therapy
    - Urine testing
    - Patient education
    - Patient contact
      - Email, phone calls
- Note
  - Doctors' reluctant use
  - Methadone accounts for less than 5% prescribed opioids and 30% of all opioid deaths

Prescription Drug Monitoring Programs PDMP

- States Implemented
  - Electronic databases created and overseen at the state level to collect data on opioids and other controlled substances as well as non-controlled drugs with potential for abuse
- Designed to
  - Monitor prescribing and dispensing to individual patients
  - Report history of treatment
  - Provide information to doctors, 3rd parties, law enforcement
  - Decrease admissions and doctor shopping

Components of Best Practices Associated With Prescribing Chronic Opioid Therapy

1. Diagnosis
2. Results of physical examination
3. Any previous history of significant pain
4. History of alternate treatments for pain
5. Potential for substance abuse
6. Coexisting disease or medical conditions
7. Presence of a medical indication or contraindication against the use of controlled substances
8. Routine use of urine drug screening
9. Prescription Monitoring Program report is appropriate
10. Controlled Substance Agreement is signed

The Sin of Over-prescription

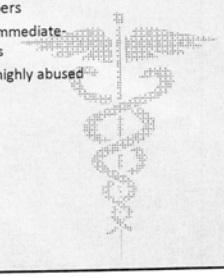
- CDC found:
  - Physicians, other Health Professionals have overestimated the benefits of opioids and underestimated the risks
  - We assumed without adequate evidence they would work well long term as they did short term
  - Pharmaceutical companies aggressively marketed opioids
  - By 2012, 259 million prescriptions were written
  - Purdue Pharma says it is committed to be a part of the solution

New Face of Epidemic

- In 2016, CDC recommends :
  - Clinicians drug test patients before and during opioid therapy to ensure medications are taken properly
  - A dosage limit of 3 days
  - National Safety Council found 99% of physicians are still prescribing beyond the recommended dosage limit

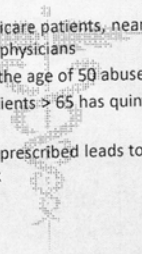
Opioid Menace

- Dentists As Prescribers
  - Prescribe 12% of immediate-release (IR) opioids
  - One of the forms highly abused



New Face of the Epidemic

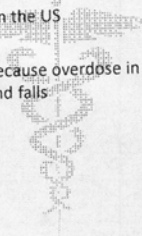
- In 2015:
- Almost one-third of all Medicare patients, nearly 12 million people, were prescribed opioids by physicians
- 2.7 million Americans over the age of 50 abused these drugs
- Hospitalization rates for patients > 65 has quintupled over the past 2 decades
- The ways opioids are often prescribed leads to physiological dependence within 1 week



New Face of Opioid Abuse

Nearly 14,000 people over the age of 45 died from overdose
42% of all such deaths in the US

Actual numbers are higher because overdose in older adults are often mislabeled as heart failure and falls



Need for Elderly Treatment Options

- Urgent need for more treatment centers geared towards the older patients:
  - Age and generation appropriate facility
  - With increased age, increase in risk of dependency
  - Patients have more serious pain
    - Decreased kidney, liver function as age increases leads to increase time drug remains in the system
    - Increased memory loss with age makes it harder to manage meds effectively

Top Ten States

- In 2015, According to the Kasier Family Foundation, 22,598 Americans died from overdoses
- States with highest rate of deaths/100, 000
  - West Virginia (28.9)
  - New Hampshire (28)
  - Rhode Island (19.8)
  - Massachusetts (17)
  - Ohio (16.4)
  - Maine (16.3)
  - Kentucky (15.3)
  - Utah (15.1)
  - Tennessee (13.1)
  - Maryland (12.2)

New Dealers

- "Older Americans are selling prescriptions for Opioids to drug dealers to raise needed cash"
- According to the National Association of Drug Diversion Investigators
  - They can make $20 per pill on the street thus increasing the temptation to increase income
  - They sell, share their meds through networks of friends and family members. Especially in the rural communities.
    - Example: Jan, 2017, 74 y.o. in TN was sentenced to probation for selling >100 oxycodone pills from her home
  - Hard to gauge the size of the problem; because, prosecutors are reluctant to prosecute elderly

New Dealers

- 1 out of 10 prescription drug case involves older adults
- A patient prescribed 3 tabs/day can make up to $3,600/month selling them.
- Elderly are new recruits for drug dealers
- Elderly pills are often taken by home healthcare workers, taken out of cabinets by family members, or just given away

More Drugs, More Problems

- New Drug Cocktails
  - Gray Death
    - Components
      - Heroin, mixed with fentanyl (50X) and add a dash of carfentanyl (100X)
  - Pink
    - Synthetic opioid called U47700 also known as "U4" or "Pink"
    - Caused 46 deaths in 2015
    - 2016 found in NY, New Hampshire, Ohio, Texas, Wisconsin and North Carolina
  - Other Cocktails
    - Heroin, fentanyl, or various fentanyl-class drugs along with cocaine, methamphetamines and THC found in marijuana

More Drugs, More Problems

- New Cocktails

  Purchase price: $10-20 on the street

  According to the Journal of the American Pharmacists Association

  massive doses of antidiarrheal (imodium) loperamide is used as alternative to opioid abuse.

  addicts who can't get heroin or opioids use > 100 capsules of loperamide to avoid withdrawal symptoms

Loperamide

- In large quantities
  - Can cross the blood brain barrier and cause euphoria or a "high"
  - Causes the heart to beat abnormally which can result in death
  - In contrast to prescription opioids which results in difficulty breathing (usually resolved with Naloxone) Loperamide toxicity is primarily in the heart, abnormal heart arrhythmias can't be reversed with Naloxone
- Patients at highest risks, young males with history of substance abuse

How do we Minimize Abuse

- Administration
  - Prescriptions
  - Parameters of Care
  - Drug class quantity limits
- Education
  - Professionals
  - Patients
- Point of Care
- Legislation

Pharmaceutical Steps to Minimize Abuse

- Abuse-Deterrent Formulations
  - Physical Barriers
    - Designed to be resistant to physical or chemical tampering
    - Examples on the market
      - Exalgo (ER Hydromorphone)
        - Will turn into hydrogel when exposed to moisture
        - Isn't easily crushed or extracted

Pharmaceutical Barriers

- Chemical Barriers
  - Created through the incorporation of an antagonist into opioid formulation
    - Market example
      - Naloxone
        - If tampered with, decreased effects of opioid and can induce withdrawal
        - Drug
          - Talwin NX
            - 50 mg. Pentazocine and 5 mg. of Naloxone

Pharmaceutical Barriers

- Aversion Barrier
  - Additional substance is incorporated into formulation with the intent to produce unpleasant effects if taken non- orally
  - Market example
    - Capzasin or niacin
      - flushing

Pharmaceutical Barriers

- ProDrug Barrier
  - Made of components that must undergo biotransformation to produce the active ingredients
    - Market Example
      - Vyvanse
        - Won't yield active ingredients if injected or snorted
      - KP201
        - Prodrug currently in development by KemPharm. Inc. and is in early phase testing

Pharmaceutical Barriers

- Routes of Administration Barrier
  - Impose physical limitations to administrations
  - Example
    - Solid Matrix Fentanyl
      - Hard to extract from patch
    - SC Buprenorphine
      - Implant placed surgically
      - Allows slow release of drug over a course of several months

Formulations Currently on the Market

- Suboxone
  - Buprenorphine/Naloxone
    - Buprenorphine
      - Only partial agonist @ Mu receptor
      - Antagonist @Kappa receptor
        - These give it a natural abuse-deterrent properties
  - Naloxone
    - Tampering with administration, using IV or IM, will trigger effects

Formulations on the Market

- Opana
  - Formulation of oxymorphone
  - Use INTAC Technology
    - Increase crush resistance properties
    - Turn into a gel when moisture present
    - Not suitable for injection
  - Exalgo
    - Developed by Mallinckrodt
    - Uses Osmotic Extended Release Delivery System (OROS)

OROS

- Semipermeable shell membrane
- Osmotically active bilayer core
- Tablets can't be easily crushed nor extracted
- Prescribed to patient who requires around the clock pain management or is opioid tolerant

Formulations on the Market

- Aversion Technology
  - Developed by Acura Pharmaceutical
  - Make extraction of active ingredients difficult by gelatinizing it when mixed with solvents (water or alcohol)
  - Difficult to grind into fine powder to snort. It irritates nasal passages causes an adverse reaction upon attempted nasal administration a burning sensation
  - Decrease excess tablet swallowing by incorporating niacin into formulation
    - Niacin
      - Flushing, itching sweating, chills begin within 15 min. after consumption and resolves between 75-90 min. later
  - Difficult to inject because it creates a gel-like substance

Aversion Strategies

Abuse Deterrent Formulation	Mechanism
Physical	Hard-shell, Hydrogel synthesis
Chemical	Opioid antagonist lessens the analgesic effects
Aversion	Produces unpleasant effects if administered non orally
ProDrug	Compounds must undergo biotransformation to produce Active ingredients
Route of Administration	Administration makes it difficult to extract
Combination	Combining 2 or more abuse deterrent formulations

Formulations in Development

- Acuracet (Acura Pharmaceutical)
  - Oxycodone/apap
  - IR formulation
  - Transitioning back to Acura by Pfizer
- Vycavert
  - Hydrocodone bitartate/apap
  - IR formulation
  - Utilizes Aversion Technology
  - Reduces nasal or injectable abuse

Formulations in Development

- DETERx Technology
  - Collegium Pharmaceuticals
  - Aims to maintain ER properties of drug even when tampered with
  - Consists of a small bead inside of capsule
- Bio-MD (Bio-Activated Molecular Delivery & Multi-pill abuse Resistance Technology)
  - Signature Therapeutics
  - Opioid is released only when medicine moves thru small intestine
  - Formulated with amino acid mask that is cleaved off by the enzyme, trypsin
  - Prevents desired "high" if taken IV

BIO-MD Technology

- Crushing, chewing, dissolving does not increase systemic exposure
- Drug
  - NKTR181
    - Nektar Therapuetics
    - Accepted into FDA Fastrack
    - Mu-opoid analgesic similar to oxycodone
    - Decrease abuse by entering CNS 90% more slowly than traditional opioids

Formulations in Development

Formulation	Developer
KP201 (IR Hydrocodone)	Kem Pharmaceutical
KP214 (ER Hydrocodone)	Kem
KP511 (IR Hydromorphone)	Kem
HYD (ER Hydrocodone)	Purdue
TD Hydrocodone (ER Hydrocodone)	Teva/CIMA labs

Conclusion

- Opioids are among the most effective meds for moderate to severe pain
- Accepted in treatment for chronic cancer pain
- Controversial for long-term use in chronic non-cancer pain
- Despite consensus of pain specialists concern exists that the pendulum has swung from under- treatment to over-treatment
- Increase prevalence of drugs directly proportional increase prescription abuse
- Doctors dual responsibility of providing balance between analgesia, side effects and other favorable outcomes while concurrently assessing and managing risk associated with abuse, addiction and diversion
- Get focused on ID best Treatment practices

Conclusion

- Pharmacists
  - Provide an important point of contact with patients from which they can educate.
  - ID problems, monitor therapy and communicate with other healthcare professionals about patients use

Conclusion

T.H.I.N.K. Framework for Opioid Medication Prescribing

T: take advantage of all resources
- UDS, BOP PDMP reports
- FDA REMS Guidelines
- missed appointments
- patient treatment agreements

H: have data in hand
- VAS (function, pain, sleep)
- UDS
- BOP PDMP reports
- opioid screening tools

I: intuition
- does this make sense
  - SARS or Something Ain't Right Syndrome
- systematic process

N: "NO" is a valid answer, do the NEXT RIGHT thing

K: know the basics of chronic medication management
- this seems to be forgotten with opioid use
- federal, state, and local laws

Developed by Ernest J. Dole, PharmD, PhC, FASHP, BCPS

BOP PDMP = Board of pharmacy prescription drug monitoring program; FDA REMS = U.S. Food and Drug Administration Risk Evaluation and Mitigation Strategy; UDS = urine drug screening; VAS = Visual Analog (Pain) Scale

Website
List of ER/LA Opioid products

- Products required to have REMS
  - USFDA website
    - Drugs/Drug safety/information by drug class/UCM348818.pdf

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.

2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

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

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release / long-acting (ER/LA) opioids.

5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to 50 morphine milligram equivalents (MME) or more per day, and should avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day.

6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed.

7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/d), or concurrent benzodiazepine use are present.

9. 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 dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.

10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.

11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder. All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation (designated category B, with individual decision making required); detailed ratings of the evidence supporting the recommendations are provided in the full guideline publication.

Source: CDC Guideline for Prescribing Opioids for Chronic Pain, 2016 in *JAMA*, April 19, 2016, p. 1638.

Drugs.com
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Medications for Pain

What is Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Medications to treat Pain

The following list of medications are in some way related to, or used in the treatment of this condition.

Drug name	Rx / OTC	Pregnancy	CSA	Alcohol	Reviews	Rating	Popularity
tramadol	Rx	C	4	X	515 reviews	6.0	
Norco	Rx	C	2	X	138 reviews	7.0	
gabapentin OFF LABEL	Rx	C	N	X	241 reviews	6.0	
Vicodin	Rx	C	2	X	100 reviews	7.0	
Dilaudid	Rx	C	2	X	214 reviews	8.0	
oxycodone	Rx	N	2	X	399 reviews	8.0	
OxyContin	Rx	N	2	X	191 reviews	8.0	
ibuprofen	Rx/OTC	C	N	X	30 reviews	7.0	
acetaminophen / hydrocodone	Rx	C	2	X	452 reviews	7.0	
Lortab	Rx	C	2	X	89 reviews	7.0	
Percocet	Rx	C	2	X	174 reviews	8.0	
Tylenol	Rx/OTC	C	N	X	8 reviews	6.0	
acetaminophen	Rx/OTC	C	N	X	28 reviews	7.0	
Celebrex	Rx	C	N		57 reviews	7.0	
hydrocodone	Rx	C	2	X	103 reviews	6.0	
Ultram	Rx	C	4	X	114 reviews	6.0	
Toradol	Rx	C	N	X	132 reviews	7.0	

Drug name	Rx / OTC	Pregnancy	CSA	Alcohol	Reviews	Rating	Popularity
naproxen	Rx/OTC	C	N	X	62 reviews	6.0	
Paracetamol	Rx/OTC	C	N	X	4 reviews	6.0	
Nucynta	Rx	C	2	X	208 reviews	6.0	
acetaminophen / oxycodone	Rx	C	2	X	376 reviews	8.0	
Demerol	Rx	C	2	X	53 reviews	9.0	
amitriptyline	Rx	C	N	X	160 reviews	7.0	
Tylenol with Codeine #3	Rx	C	M	X	82 reviews	5.0	
Roxicodone	Rx	N	2	X	28 reviews	9.0	

Topics under Pain

- **Back Pain** (229 drugs in 5 topics)
- **Breakthrough Pain** (6 drugs)
- **Chronic Myofascial Pain** (33 drugs)
- **Chronic Pain** (83 drugs)
- **Costochondritis** (32 drugs)
- **Dercum's Disease** (2 drugs)
- **Epicondylitis, Tennis Elbow** (16 drugs)
- **Fibromyalgia** (33 drugs)
- **Headache** (290 drugs in 7 topics)
- **Lhermitte's Sign** (1 drug)
- **Muscle Pain** (192 drugs in 2 topics)
- **Neck Pain** (71 drugs in 2 topics)
- **Neuralgia** (78 drugs in 8 topics)
- **Nocturnal Leg Cramps** (18 drugs)
- **Pain/Fever** (162 drugs in 2 topics)
- **Postoperative Pain** (7 drugs)
- **Reflex Sympathetic Dystrophy Syndrome** (10 drugs)
- **Somatoform Pain Disorder** (12 drugs)
- **Vulvodynia** (19 drugs)

Alternative treatments for Pain

The following products are considered to be alternative treatments or natural remedies for Pain. Their efficacy may not have been scientifically tested to the same degree as the drugs listed in the table above. However there may be historical, cultural or anecdotal evidence linking their use to the treatment of Pain.

Legend

Off Label	This medication may not be approved by the FDA for the treatment of this condition.

Prescription Only / Over the Counter

Rx	Prescription Only
OTC	Over the Counter
Rx/OTC	Prescription or Over the Counter

Pregnancy

A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use in pregnant women clearly outweigh potential benefits.
N	FDA has not classified the drug.

Controlled Substances Act Schedule

N	Is not subject to the Controlled Substances Act.
1	Has a high potential for abuse. Has no currently accepted medical use in treatment in the United States. There is a lack of accepted safety for use under medical supervision.
2	Has a high potential for abuse. Has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. Abuse may lead to severe psychological or physical dependence.
3	Has a potential for abuse less than those in schedules 1 and 2. Has a currently accepted medical use in treatment in the United States. Abuse may lead to moderate or low physical dependence or high psychological dependence.
4	Has a low potential for abuse relative to those in schedule 3. It has a currently accepted medical use in treatment in the United States. Abuse may lead to limited physical dependence or psychological dependence relative to those in schedule 3.
5	Has a low potential for abuse relative to those in schedule 4. Has a currently accepted medical use in treatment in the United States. Abuse may lead to limited physical dependence or psychological dependence relative to those in schedule 4.

Alcohol

X	Interacts with Alcohol.

UNC Health Care Guideline

Opiate Equianalgesic Dosing Chart

University of North Carolina Hospitals
Pharmacy & Therapeutics Committee

Dosing Table for Opioids

Drug	Oral to Parenteral (IM, SQ, IV) Ratio	Approximate equianalgesic dose	ADULTS Recommended starting dose (adults more than 50 kg body weight)		PEDIATRICS Recommended starting dose (children and adults less than 50 kg body weight)[1] NOTE: when assessing doses in larger children, note usual initial adult dose	
			oral	parenteral	oral	parenteral
Opioid Agonist						
Morphine	3 mg oral to 1 mg parenteral	10 mg PARENTERAL	10-20 mg every 4 hours	3-5 mg every 4 hours	0.3-0.5 mg/kg/dose every 6 hours	0.05-0.2 mg/kg/dose every 4 hours (MAX 2-4 mg)
Codeine[2,3] (as Tylenol #3: 30 mg codeine/300 mg APAP)	1.7 mg oral to 1 mg parenteral	Use of parenteral codeine is not recommended.	30-60 mg Every 4 hours	N/A	0.5-1.5 mg/kg/dose every 6 hours	N/A
Fentanyl	N/A	Fentanyl 100 mcg (0.1 mg) PARENTERAL = Morphine 10 mg PARENTERAL (see next Table for conversion from fentanyl patches to parenteral morphine)	Actiq™, Fentora™ are not available at UNC.	50 mcg every 2 hours	N/A	1 – 2 mcg/kg/dose every 4 hours
Hydrocodone[3] (as Norco: 5 mg hydrocodone/325 mg APAP)	N/A	Hydrocodone 1 mg ORAL is equal to Morphine 1 mg ORAL	5-10 mg every 4 hours	N/A	0.05-0.2 mg/kg/dose every 4 hours	N/A
Hydromorphone (Dilaudid)	5 mg oral to 1 mg parenteral	Hydromorphone 2 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL	2 mg every 4 hours	1 mg every 4 hours	0.03-0.08 mg/kg/dose every 4 hours	0.015 mg/kg/dose every 4 hours
Meperidine	4 mg oral to 1 mg parenteral	Meperidine 75 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL	NOT RECOMMENDED AS AN ANALGESIC (FOR TREATMENT OF RIGORS ONLY)			
Methadone[4]	Caution is advised when converting to methadone due to variability in patient response and delayed peak effects. Reliable equianalgesic conversion for repeated dosing is not available. Parenteral methadone is not available at UNC.		5 mg every 8 hours	N/A	0.1 mg/kg/dose every 8 hours	N/A
Oxycodone[3] (as Percocet: 5 mg oxycodone/325 mg APAP)	N/A	Oxycodone 1 mg ORAL is equal to Morphine 1.5 mg ORAL	5 -10 mg every 4 hours	N/A	0.05-0.2 mg/kg/dose every 6 hrs	N/A
Opioid Agonist-Antagonist and Partial Agonist						
Butorphanol	N/A	Butorphanol 2 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL	N/A	2 mg every 4 hours	N/A	10-20 mcg/kg/dose every 4hours
Nalbuphine	N/A	Nalbuphine 10 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL	N/A	10 mg every 4 hours	N/A	0.1 mg/kg/dose every 4 hours

Note: Published tables vary in the suggested doses that are equianalgesic to morphine. Clinical response is the criterion that must be applied for each patient; titration to clinical response is necessary. Due to cross-tolerance, when switching from one opioid to another, the starting dose of the new opiod should be 50% to 67% of the equianalgesic dose except when switching to methadone. When switching to methadone, the starting dose should be 10% to 25% of the equianalgesic dose. Opioid dose should then be titrated and individualized to clinical situation and patient response. When using higher total doses, decrease total dose incrementally by 30% per day.

[1]**Caution**: Doses listed for patients with body weight less than 50kg cannot be used as initial starting doses in babies less than 6 months of age.
[2]**Caution**: Codeine doses above 65 mg often are not appropriate due to diminishing incremental analgesia with increasing doses but continually increasing side effects.
[3]**Caution**: Doses of aspirin and acetaminophen in combination opioid/NSAID preparations must also be adjusted to the patient's body weight.
[4]**Caution**: Methadone is appropriate for chronic stable pain in an opioid-tolerant patient, but is usually avoided in opiate-naïve patients. Convert & titrate slowly (over 3-6 days) due to long biphasic half-life; beware of cumulative effects in first 3-10 days.

Updated: December 2009.

UNC Health Care Guideline

Opiate Equianalgesic Dosing Chart

University of North Carolina Hospitals
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Morphine to Transdermal Fentanyl Equivalency	
Parenteral Morphine Dose (mg/24 hours)	**Fentanyl Patch dose (mcg/hr)**
4-11	12
8-22	25
23-37	50
38-52	75
53-67	100
68-82	125
83-97	150
98-112	175
113-127	200

NOTE: Do NOT cut patch.

[1]**Caution**: Doses listed for patients with body weight less than 50kg cannot be used as initial starting doses in babies less than 6 months of age.
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