OPIOIDS AND PAIN MANAGEMENT

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Physical Medicine & Rehabilitation
What is the most common reason someone sees a doctor?
Pain is the most common reason a person seeks care from a physician.

Up to ninety percent of all Americans regularly experience acute or chronic pain.

One third of all Americans will experience chronic pain during their lifetime.
What is pain?
Pain = An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

*International Association for the Study of Pain (IASP) – Committee on Taxonomy 1979*
In reality, pain is whatever the patient says it is. It is always relative and highly subjective.
Pain is more than nociception
Psychological & Social Factors
- Sex & Gender
- Age
- Cognitive Level
- Previous Pains
- Family Learning
- Culture

Emotional Factors
- Fear
- Anger
- Frustration

Noxious Stimulus

Situational Factors
- Expectation
- Control
- Relevance

Brain

Pain
Acute vs. chronic

- 3 months
- Or timeframe of expected recovery
Pain can change from an acute, adaptive phenomenon to a pathological, maladaptive, chronic state.

- Chronic pain is now considered a chronic disease and not just a symptom.
- A mix of changes in peripheral input and central pain processing.
  - Many chronic pain conditions do not have an identifiable precipitating event.
Opioid Statistics

- USA is 4.6% of world population
  - USA consumes 80% of the world’s opioids
  - USA consumes 99% of the world’s hydrocodone

Why? It is complicated
Most opioids are prescribed by Primary Care Clinicians
Family Practitioners (28.8%)
Internists (14.6%)
Dentists (8%) – Largest group of prescribers age 10-19

Most prescriptions were for hydrocodone and oxycodone containing products (84.9%, 67.5 million)

These were issued for short treatment courses (19.1% for 2 weeks, 65.4% for 2-3 weeks)

Opioid Prescriptions by State 2012 vs 2016
Opioid Prescriptions 2012 vs 2016
Opioid Prescription by City 2012 vs 2016
<table>
<thead>
<tr>
<th>Year</th>
<th>Total Number of Prescriptions</th>
<th>Prescribing Rate Per 100 Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>215,917,663</td>
<td>72.4</td>
</tr>
<tr>
<td>2007</td>
<td>228,543,773</td>
<td>75.9</td>
</tr>
<tr>
<td>2008</td>
<td>237,860,213</td>
<td>78.2</td>
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<tr>
<td>2009</td>
<td>243,738,090</td>
<td>79.5</td>
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<tr>
<td>2010</td>
<td>251,088,904</td>
<td>81.2</td>
</tr>
<tr>
<td>2011</td>
<td>252,167,963</td>
<td>80.9</td>
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<tr>
<td>2012</td>
<td>255,207,954</td>
<td>81.3</td>
</tr>
<tr>
<td>2013</td>
<td>247,090,443</td>
<td>78.1</td>
</tr>
<tr>
<td>2014</td>
<td>240,993,021</td>
<td>75.6</td>
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<tr>
<td>2015</td>
<td>226,819,924</td>
<td>70.6</td>
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<tr>
<td>2016</td>
<td>214,881,622</td>
<td>66.5</td>
</tr>
<tr>
<td>2017</td>
<td>191,218,272</td>
<td>58.7</td>
</tr>
</tbody>
</table>
☐ How would you rate your Pain Management education at your medical school?
Over 80% of physicians rate their medical school education about chronic pain treatment as inadequate

33% of PCPs screen for substance abuse

16.9% view themselves as “very prepared” to detect aberrant drug-related behavior

30.2% see themselves as “very prepared” to detect prescription drug abuse


Opioid Abuse

- What is the difference between:
  - Misuse?
  - Abuse?
  - Diversion?
From whom would someone obtain opioids?
# Top Drugs among 8th and 12th Graders, Past Year Use

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>8th Graders</th>
<th>12th Graders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illicit drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana/Hashish</td>
<td>11.7%</td>
<td></td>
</tr>
<tr>
<td>Inhalants</td>
<td>5.3%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Synthetic Marijuana</td>
<td>3.3%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Cough Medicine</td>
<td>2.0%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Tranquilizers</td>
<td>1.7%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Adderall</td>
<td>1.3%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>1.3%</td>
<td>4.3%</td>
</tr>
<tr>
<td>OxyContin</td>
<td>1.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Vicodin</td>
<td>1.0%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Cocaine (any form)</td>
<td>1.0%</td>
<td>3.3%</td>
</tr>
<tr>
<td>MDMA (Ecstasy)</td>
<td>0.9%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Ritalin</td>
<td>0.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Only 12th graders surveyed about sedatives use

Source: University of Michigan, 2014 Monitoring the Future Study
More Opioid Statistics
RISE IN OPIOID OVERDOSE DEATHS IN AMERICA

A Multi-Layered Problem in Three Distinct Waves

351,000 people died from an opioid overdose (1999-2016)

- 1990s marked a rise in prescription opioid overdose deaths
- 2010 marked a rise in heroin overdose deaths
- 2013 marked a rise in synthetic opioid overdose deaths

Rx OPIOIDS
- Include natural, semi-synthetic, and synthetic and can be prescribed by doctors

HEROIN
- An illegal opioid

SYNTHETIC OPIOIDS
- Such as fentanyl and tramadol are very powerful and can be illegally made

Learn more about the evolving opioid overdose crisis: www.cdc.gov/drugoverdose
3 Waves of the Rise in Opioid Overdose Deaths

Calculating each wave of rise in mortality:

**Wave 1: Rise in Prescription Opioid Overdose Deaths**

**Wave 2: Rise in Heroin Overdose Deaths**

**Wave 3: Rise in Synthetic Opioid Overdose Deaths**

Overdose Death Rates Involving Opioids, by Type, United States, 2000-2016

Age-adjusted rate* of drug overdose death†, by state—2010 and 2016§

Deaths per 100,000 population

West Virginia
Ohio
New Hampshire
District of Columbia
Pennsylvania
Kentucky
Maryland
Massachusetts
Delaware
Rhode Island
Maine
Connecticut
New Mexico
Tennessee
Michigan
Indiana
Florida
Missouri
New Jersey
Utah
Vermont
Louisiana
Nevada
Oklahoma
Arizona
North Carolina
Wisconsin
Illinois
South Carolina
New York
Wyoming
Alaska
Virginia
Colorado
Alabama
Idaho
Washington
Arkansas
Georgia
Hawaii
Minnesota
Mississippi
Oregon
Montana
California
Kansas
Iowa
North Dakota
Texas
South Dakota
Nebraska

2016 rate = 2010 rate

*Age-adjusted rates are adjusted to the 2000 standard U.S. population.
†Drug overdose deaths include deaths from misuse of and dependencies on prescription opioids, heroin, and fentanyl.
§Data for District of Columbia, New Hampshire, and West Virginia are provisional and subject to change.
National Overdose Deaths
Number of Deaths from Prescription Opioid Pain Relievers

Source: National Center for Health Statistics, CDC Wonder

National Overdose Deaths
Number of Deaths from Heroin

Source: National Center for Health Statistics, CDC Wonder
Figure 3. Number of opioid-analgesic poisoning deaths, by involvement of benzodiazepines: United States, 1999–2011

NOTE: Access data table for Figure 3 at: http://www.cdc.gov/nhts/data/databriefs/db166_table.pdf#3.
An estimated 88,000 people (approximately 62,000 men and 26,000 women) die from alcohol-related causes annually.

In 2014, alcohol-impaired driving fatalities accounted for 9,967 deaths (31 percent of overall driving fatalities).
For every 1 death there are...

- 10 treatment admissions for abuse
- 32 emergency dept visits for misuse or abuse
- 130 people who abuse or are dependent
- 825 nonmedical users
How would you identify an individual that is abusing or diverting opioids?
Recognizing Nonmedical Users of Prescription Drugs

- Unusual behavior in the waiting room
- Assertive personality, demanding immediate action
- Unusual appearance: extremes of slovenliness or overdressed
- Shows unusual knowledge of controlled substances and/or gives textbook symptoms or vague, evasive medical history
- No regular doctor, often no health insurance
- Has no interest in diagnosis
- Fails to keep appointments for further diagnostic tests or refuses to see another practitioner for consultation

Aberrant drug-related behaviors suggesting addiction in pain patients (Portenoy & Payne 1997):

- Selling or forging prescriptions
- Altering route of administration
- Obtaining prescriptions from non-medical sources
- Dose escalations or failure to comply with regimen
- Frequently losing medication
- Seeking Rx from other MDs
- Deterioration in function
- Resisting changes despite adverse effects

- Probably more predictive
  - Selling prescription drugs
  - Prescription forgery
  - Stealing or borrowing another patient’s drugs
  - Injecting oral formulation
  - Obtaining prescription drugs from non-medical sources
  - Concurrent abuse of related illicit drugs
  - Multiple unsanctioned dose escalations
  - Recurrent prescription losses

- Probably less predictive
  - Aggressive complaining about need for higher doses
  - Drug hoarding during periods of reduced symptoms
  - Requesting specific drugs
  - Acquisition of similar drugs from other medical sources
  - Unsanctioned dose escalation 1 –2 times
  - Unapproved use of the drug to treat another symptom
  - Reporting psychic effects not intended by the clinician
30.4% of chronic pain patients in a large (N=239) general practice reported taking extra narcotic doses (Rosser et al. 2011)
Steps Taken by Physicians to Avoid Diversion

- Percentage of physicians did the following:
  - Limit 30-day supply to those compliant – 75%
  - Prescribe lowest effective dose – 64%
  - Require drug screening – 62%
  - Highly selective of patients – 49%
  - Require counseling if indicated -- 43%
  - Require more than monthly visits – 35%
  - Random pill counts – 32%
  - Ask family to observe ingestion

Universal Precautions in Opioid Analgesic Therapy

- Uniform approach reduces stigma and risk, improves care
- Ask patients about personal and family history of substance abuse
- Obtain consent with formal written treatment agreement
- Medication agreements specify parameters for adherence, means of testing compliance, and goals
- Ongoing reassessment of benefits from trial of opioid therapy and complete documentation

Opioid Prescribing

- Documentation
- Protocols
- Monitoring
Pain Management Protocol

- Familiarize with the management options
- Decide what you are comfortable with
- Write down the protocol
- Do not deviate from the protocol
- Do not wait until you are uncomfortable or reached the limits of the protocol before referring out
What are important details to document?
Documentation

- Proper diagnosis
  - “LBP” is not a diagnosis
- Goals of treatment
  - Increase function
  - Palliative care
  - Increase social, community and workplace interactions
  - Proper use of medications
- 4 As
  - Activity
  - Analgesia
  - Adverse reactions
    - Falls? Problems driving?
  - Aberrant behavior
- Another 2 As
  - Adherence to therapy
  - Affect
Documentation

- Monitoring
- Compliance of diagnostic and treatment plans
- Opioid treatment agreement and consent
- Outside records
  - Preferably from the source and not the patient
- Make a copy of valid state issued ID with current address
### Opioid Risk Tool

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Illicits</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>- Alcohol</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>- Prescription Drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Personal History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Illicits</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>- Alcohol</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>- Prescription Drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Age (16-45)</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>History of Pre-Adolescent Sexual Abuse</strong></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychological Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Schizophrenia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>- ADHD</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>- OCD</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>- Bipolar</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>- Depression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Administer prior to starting opioid therapy
- Low Risk 0-3
- Mod Risk 4-7
- High Risk 8 or higher
- Has anyone in your family needed to be treated for substance abuse?
- Have you ever thought or has anyone mentioned that you may need treatment?
Assessment of Opioid Abuse

- Prescription Drug Use Questionnaire (PDUQ) (Compton et al. 1998):
  - Hoarding pills
  - Using analgesics to relieve symptoms other than pain
  - Supplementing with alcohol or drugs

- Pain Assessment and Documentation Tool (PADT) (Passik et al. 2004) assesses 4 domains:
  - pain relief
  - patient functioning
  - adverse events
  - drug-related behaviors
What is the role of the opioid treatment agreement?
Some patients feel they are being treated like criminals due to the opioid treatment agreement.

“The purpose of this agreement is to give you information about the medications you will be taking for pain management and to assure that you and your physician/health care provider comply with all state and federal regulations concerning the prescribing of controlled substances.”
How can you monitor patients?
Monitoring

- Random pill counts
- Prescription monitoring programs
- Urine drug screens
- “I know my patients” has been disproven as a way of monitoring
Consider:

- Pill counts on every visit
- Random pill counts

Sometimes pharmacists can agree to perform these and send documentation

Consider this if traveling for random pill count would cause a great hardship to the patient.
Prescription Monitoring Program (PMP)

- Red Flags
  - Five or more prescribers per year
  - Four or more pharmacies in 90 days
  - Forty or greater Morphine Equivalent Dose (MED) on an average and greater than 100 MED at a time.
  - History of previous reported overdose.
PMP NARx Scores

- Monitors Narcotics, Sedatives and Stimulants
- Each is scored from 000 to 999
  - Last digit is the number of active prescriptions
- Calculated by
  - Number of Prescribers
  - Number of Pharmacies
  - MED
  - Overlapping prescriptions.
PMP NARx Scores

- Most recent activity is weighted more heavily than distant activity
  - 75% of patients score less than 200
  - 19% between 200 and 500
  - 5% between 500 and 650
  - 1% above 650
- Patients may have a high score and still be within prescribers expectations.
PMP Overdose Risk Score (ORS)

- Scored from 000 to 999
- Risk of unintended overdose is higher the higher the score
- History of reported overdose is scored as 99x
  - X being the number of reported overdoses.
  - Example: Five reported overdoses = 995
**ORS (Brief Table)**

<table>
<thead>
<tr>
<th>Score</th>
<th>MED</th>
<th>Overdose Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>010-450</td>
<td>Less than 50</td>
<td>1-25</td>
</tr>
<tr>
<td>450-650</td>
<td>Between 50 and 90</td>
<td>25-85</td>
</tr>
<tr>
<td>Greater than 650</td>
<td>Greater than 90</td>
<td>85-329</td>
</tr>
</tbody>
</table>

- ORS is weighted differently than NARx.
- For example, number of pharmacies has a higher weight than MED.
What are the strengths and weaknesses of urine drug screens?
Urine Drug Testing

- Monitor use of prescribed medications
- Identify use of non-prescribed medications or illicit substances
- May increase the safety of prescribing medications by identifying the potential for misuse, or abuse
- Monitor compliance in a patient with a known substance use disorder
Different types of UDT

- **Immunoassay**
  - **Strengths:**
    - In-Office Screen (Dip stick)
    - Results in minutes
    - May help with preliminary treatment decisions
  - **Weaknesses:**
    - Only detects drug classes & some substances
    - Not very sensitive
    - High incidence of false positives & false negatives
Different types of UDT

- Laboratory-based Quantitative Testing
- Gas/Liquid Chromatography-Mass Spectrometry

**Strengths:**
- Detects specific medications, substances, and metabolites
- False positive and false negative results are rare
- Quantitative results

**Weaknesses:**
- Detects specific medications, substances, and metabolites
- Results could be misinterpreted by a less experienced practitioner
- Results can take days
Performed UDT on 470 patients

Eight prescribing physicians

They “knew” their patients

Inconsistent UDT were defined as:

- Absence of prescribed opioids
- Presence of non-prescribed controlled substance
- Presence of illicit substance
- Adulterated sample
### Inconsistent Urine Drug Screen Percentages

<table>
<thead>
<tr>
<th>Results</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of prescribed opioids</td>
<td>10.2%</td>
</tr>
<tr>
<td>Presence of non-prescribed controlled substance</td>
<td>14.5%</td>
</tr>
<tr>
<td>Presence of illicit substance</td>
<td>17.6%</td>
</tr>
<tr>
<td>Adulterated sample</td>
<td>2.6%</td>
</tr>
<tr>
<td>Consistent Results</td>
<td>55%</td>
</tr>
</tbody>
</table>
Inconsistent result?

- What medications is the patient taking?
  - What are the medication metabolites?
- When was the last time the patient took the medication?
- Is the patient taking medications (prescribed or OTC) that we are not aware of?
- Could the result be a false positive or false negative?
- Could the results be explained by different drug metabolism?
- Could it be due to drug-drug interactions?
How would you assess pain?
Pain Assessment

- Onset
- Location/Site
- Temporal profile
- Quality
- Unpleasantness
- Distress
- Associated Symptoms

Psychological
- Aggravating
- Alleviating
- Impact on Function
- Habits
- Coping Skills
Should we treat or manage every patient that reports pain?
“...the ethical obligation to manage pain and relieve the patient’s suffering is at the core of the health care professional’s commitment”

Carr et al. US Dept of Health and Human Services
We ARE obligated to treat pain

But...

☐ Not obligated to treat on the first visit
☐ Not obligated to treat in the absence of adequate diagnostic workup (physical/psychological)
☐ Not obligated to treat with opioids
☐ Not obligated to treat as patient specifies
☐ Not obligated to treat using only pharmacology
☐ Not obligated to treat without requiring patient involvement and responsibility
What options do we have to manage pain?
Tools of the Pain Trade

- **Non invasive**
  - Exercise
  - Cognitive Behavioral Therapy
  - Physical and Occupational Therapy
  - Chiropractic
  - Nutritional Therapy
  - Massage Therapy
  - Psychological Therapy
  - Alternative/complementary therapies

- **Invasive**
  - Medications
  - Anesthetic blocking agents
  - Neuromodulatory techniques
  - Surgery
  - Neuroablation
Therapy

- Relative bed rest
  - Discouraged
- Traction
- Physical Modalities
  - Cryotherapy
  - Heat
Transcutaneous Electrical Nerve Stimulation

- Gate control theory of pain
  - Stimulating large myelinated fibers inhibits the transmission of small unmyelinated fibers to the spinal cord
- Device with electrode pads
- May be used at work, recreational activities
- Do not use while driving
Physical Therapy

- Goals for PT
  - Decrease pain
  - Strengthen muscles
  - Stretch contracted muscles
  - Decrease mechanical stresses to spine
  - Improve fitness to prevent injury
  - Stabilize hypermobile segments
  - Improve mobility and function
  - Decrease fall risks
Example of PT for Low Back Pain

- Flexion exercises
  - To open intervertebral foramina
  - To open facet joints
  - To stretch hip flexors and back extensors
  - Strengthen abdominal and gluteal muscles
  - Increase intra-abdominal pressure to stabilize spine
Exercise

- Indications for Flexion exercises
  - Pain relief on:
    - Sitting with:
      - Repeated forward bending
      - Increased lumbar lordosis
  - Pain exacerbated on:
    - Walking
    - Standing with:
      - Sustained forward bending
      - Repeated / sustained backward bending
Example of PT for Low Back Pain

- Extension exercises
  - Strengthen paraspinal extensors
  - Improve muscle strength and standing endurance
  - Must include hamstring stretch
  - Promoting a shift of disc nuclear material to a normal position
    - Patients with acute disc herniation, multiple back surgeries, or facet joint disease may have exacerbation of pain
Exercise

- **Indication for extension exercises:**
  - Pain relief on:
    - Laying down
    - Walking with:
      - Repeated backwards bending
      - Decreased lumbar lordosis
  - Pain exacerbated on:
    - Sitting
    - Driving
    - Arising from chair
    - Stooping
    - Bending
Exercise

- Isometric flexion exercises
  - May be done supine or sitting
  - Sequence of contractions to produce a pelvic tilt
    - Abdominal muscles
    - Gluteal muscles
    - Hip adductors
  - Hold contraction for 10-15 seconds done frequently throughout the day
  - May increase duration of contractions as tolerated
Different Procedures for Pain Management

- Trigger Point Injections
- Peripheral Joint Injections
  - Anatomically guided
  - Ultrasound or Fluoroscopy
- Peripheral Nerve Blocks
  - Anatomically guided
  - Ultrasound or Fluoroscopy
  - Nerve stimulator guided
- Peripheral Nerve Stimulation
- Phenol Injections
- Botulinum Injections

- Spinal Injections
  - Epidural Steroid Injections
    - Interlaminar
    - Transforaminal
    - Caudal
  - Facet Joint Injections vs Medial Branch Blocks
    - Radio Frequency Ablation
  - Sacroiliac Joint injection
- Spinal Cord Stimulation
- Intrathecal Pumps
Pharmacological Treatment of Pain

Pharmacology – Drug Classes

A. Opiates
   1. Methadone, proproxyphene
   2. Codeine, Morphine, Oxycodone, Oxymorphone, Hydrocodone, Hydromorphone
   3. Fentanyl, meperidine
   4. Tramadol, Tapentadol

B. Non-Opiates
   1. Tricyclics and atypical antidepressants
   2. NSAIDS – COX1, COX2
   3. Steroids
   4. Antiepileptics
   5. Muscle relaxants
      - Alpha agonists
      - Benzodiazepines
# Pain Management Ladder

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>By mouth</td>
<td>(When giving pain medications, the oral route is always preferred over other routes like transdermal, intravenous or sub-cutaneous routes)</td>
</tr>
<tr>
<td>By the clock</td>
<td>(Chronic basal pain is usually best treated with scheduled long acting pain medications, with short acting pain medications on an as needed basis for incidental or break through pain)</td>
</tr>
<tr>
<td>By the ladder</td>
<td><img src="image" alt="Pain Ladder Diagram" /></td>
</tr>
</tbody>
</table>

Pain ladder from the World Health Organization
- **Opioid** describes all compounds that work at opioid receptors.

- **Opiate**: naturally occurring alkaloids:
  - morphine, codeine, thebaine, and papaverine.

- **Narcotic** was originally used to describe sleep-inducing medications, but in the United States, its usage has shifted into a legal term.
Opioid drugs include full agonists, partial agonists, and antagonists—measures of intrinsic activity or efficacy.
Opioid Metabolism

- Good absorption through subcutaneous, intramuscular, and oral routes.
  - This varies depending on the molecule
- Due to first-pass effect, the oral dose of the opioid may higher than the parenteral dose to achieve the same level of analgesia.
  - Interpatient variability in first-pass opioid metabolism makes the calculation of an effective oral dose difficult.
The opioids are hepatically metabolized mostly into glucuronides which are then excreted by the kidneys.

Morphine is primarily conjugated to:

- Morphine-3-glucuronide (M3G), a compound with neuroexcitatory properties.
- Approximately 10% of morphine is metabolized to morphine-6-glucuronide (M6G), an active metabolite with analgesic potency four to six times that of morphine.
Glucuronidation

- Glucuronides are relatively polar metabolites & have limited ability to cross the blood-brain barrier.
- Retention of these metabolites produce adverse effects in patients with renal failure or when large doses of morphine are administered or high doses are administered over long periods.
  - M3G-induced CNS excitation (seizures) or enhanced and prolonged opioid action produced by M6G.
Hepatic oxidative metabolism is the primary route of the phenylpiperidine opioids (fentanyl, meperidine, alfentanil, sufentanil) leaving only small quantities of the parent compound unchanged for excretion.

- Meperidine is metabolized to normeperidine
  - In high concentrations, normeperidine may cause seizures.
No active metabolites of fentanyl have been reported.

The P450 isozyme CYP3A4 metabolizes fentanyl by N-dealkylation in the liver.

CYP3A4 is also present in the mucosa of the small intestine and contributes to the first-pass metabolism of fentanyl when it is taken orally.
Codeine, oxycodone, and hydrocodone undergo metabolism in the liver by P450 isozyme CYP2D6, resulting in stronger active metabolites.

- Codeine is demethylated to morphine which is then conjugated.
- Hydrocodone is metabolized to hydromorphone
  - Then conjugated to hydromorphone-3-glucuronide (H3G), which has CNS excitatory properties.
  - Hydromorphone cannot form a 6-glucuronide metabolite.
- Oxycodone is metabolized to oxymorphone
  - then conjugated to oxymorphone-3-glucuronide (O3G).
Genetic polymorphism of CYP2D6 has been documented and linked to the variation in analgesic and adverse responses seen among patients. Codeine itself has relatively low affinity for opioid receptors.

- Poor metabolizers may experience no significant analgesic effect as codeine is not metabolized into morphine.
- Ultra rapid metabolizers have a relative excess of morphine resulting in respiratory depression and death.
- Routine use of codeine, especially in pediatric age groups, is significantly less in the United States.
Methadone

- The synthetic opioid methadone is metabolized through several CYP450 pathways.
  - This in part accounts for its highly variable bioavailability.
- The most important hepatic pathway for metabolism is CYP2B6.
Heroin is an Ester
Rapidly hydrolyzed by plasma and tissue esterases.
Heroin (diacetylmorphine) is hydrolyzed to monoacetylmorphine and finally to morphine, which is then conjugated with glucuronic acid.
Excretion

- Polar metabolites, including glucuronide conjugates of opioid analgesics, are excreted mainly in the urine.
- Small amounts of unchanged drug may also be found in the urine.
- Glucuronide conjugates are found in the bile
  - Enterohepatic circulation is only a small portion of the excretory process of opioids.
# Adverse Effects of Opioids

<table>
<thead>
<tr>
<th>Adverse Effects with Acute Use</th>
<th>Adverse Effects with Chronic Use</th>
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</thead>
<tbody>
<tr>
<td>Respiratory depression</td>
<td>Hypogonadism</td>
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<tr>
<td>Nausea / vomiting</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Increased feeding</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Increased growth hormone secretion</td>
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<tr>
<td>Constipation</td>
<td>Withdrawal effects</td>
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<tr>
<td>Urinary retention</td>
<td>Tolerance, dependence</td>
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<tr>
<td>Delirium</td>
<td>Abuse, addiction</td>
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<tr>
<td>Sedation</td>
<td>Hyperalgesia</td>
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<tr>
<td>Myoclonus</td>
<td>Impairment while driving</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
</tbody>
</table>
## Opioid Drug Interactions

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Interaction with Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedative-hypnotics</td>
<td>Increased central nervous system depression, particularly respiratory depression.</td>
</tr>
<tr>
<td>Antipsychotic agents</td>
<td>Increased sedation. Variable effects on respiratory depression. Accentuation of cardiovascular effects (antimuscarinic and α-blocking actions).</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Relative contraindication to all opioid analgesics because of the high incidence of hyperpyrexial coma; hypertension has also been reported.</td>
</tr>
</tbody>
</table>
Opioid Tolerance

- **Opioid tolerance** is the phenomenon whereby repeated doses of opioids have a diminishing analgesic effect.

- Development of tolerance begins with the first dose of an opioid,
  - may not clinically manifest until after 2–3 weeks of frequent exposure to ordinary therapeutic doses.

- Tolerance develops when large doses are given at short intervals.
Opioid Tolerance

- Tolerance may develop to the analgesic, sedating, and respiratory depressant effects of opioid agonists

- Cross-tolerance
  - Patients tolerant to one opioid often show a reduction in analgesic response to other agonist opioids
  - This cross tolerance is incomplete therefore, there is risk of sedation and respiratory depression
Physical Dependence

- The development of physical dependence is an accompaniment of tolerance to an opioid.
- Failure to continue administering the drug results in a characteristic withdrawal or abstinence syndrome
  - Reflects an exaggerated rebound from the acute pharmacologic effects of the opioid.

- Signs and symptoms of withdrawal:
  - Rhinorrhea
  - Lacrimation
  - Yawning
  - Chills
  - Piloerection
  - Hyperventilation
  - Hyperthermia
  - Mydriasis
  - Muscular aches
  - Vomiting
  - Diarrhea
  - Anxiety
Addiction

- As defined by the American Society of Addiction Medicine, addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry.

- Characterized by:
  - Inability to abstain consistently
  - Impairment in behavioral control
  - Craving
  - Diminished recognition of significant problems with one’s behaviors and interpersonal relationships
  - Dysfunctional emotional response
Opioids: Phenanthrenes

- Representative drug: Morphine
- Similar drugs:
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Hydromorphone
  - Levorphanol
  - Oxymorphone
  - Heroin
  - Naloxone

- Nalbuphine (Nubaine,m)
- Butorphanol (Stadol,m)
- Buprenorphine (Bupronex,p)

- p=partial agonist
- m=mixed
Opioids: Benzomorphans

- Representative drug: Pentazocine (Talwin, m)
- Similar drugs:
  - Diphenoxylate (lomotil)
  - Loperamide
Opioids: Phenylpiperidines

- Representative drug: Meperidine (Demerol)

- Similar drugs:
  - Fentanyl
  - Sufentanyl
  - Alfentanil
  - Remifentanil
- Representing drug: Methadone
- Similar drugs:
  - Propoxyphene
Tramadol

- Partial mu agonist, serotonin and norepinephrine reuptake inhibitor
- Risk for seizures
- May be helpful for neuropathic pain due to multiple areas of action.
Tapentadol

- Partial mu agonist, norepinephrine reuptake inhibitor
- Schedule II opioid
- May be helpful for neuropathic pain due to multiple areas of action.
Avoid Benzos and Opioids

- Prescribe Benzos with caution.
  - Benzos and opioids are both CNS suppressants and may interact adversely.
  - Educate patient not to drink alcohol while taking opioids and/or benzos.

- On August 2016: “The FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use”
- Hydrocodone cough medicines can have 10 mg of hydrocodone per dose.
Mechanistic Approach to Pain
Descending inhibition

Brain

NE/5HT GABA
Opioid receptors

Peripheral sensitization

Terminal

PNS

Spinal cord

Central sensitization

Ca++:
NMDA:
PGE:
Subs P

PGEr
Na+ TTXr
NK-1
VR-1
NGF
Opioid r
NER

Opioid receptors

Ca++:
NMDA:
PGE:
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Descending inhibition

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Peripheral sensitization

Central sensitization

Ca^{++}: GBP; OXC Conotoxin
NMDA: Ketamine, TPM
Dextromethorphan
Methadone
PGE: NSAIDs / COX-2

TCAs
SNRIs
Opioids
Tramadol
Clonidine
Baclofen
Clonazepam

GBP; OXC Conotoxin
Ketamine, TPM
Dextromethorphan
Methadone

NSAIDs
COX-2i
Opioids
Capsaicin
Clonidine

TCA
CBZ OXC
TPM LTG
Mexiletine
Lidocaine

PGE:

Ca^{++}: GBP; OXC Conotoxin
NMDA: Ketamine, TPM
Dextromethorphan
Methadone
PGE:

NSAIDs / COX-2
Disease Modifiers

Descending inhibition

Brain
- TCAs
- SNRIs
- Opioids
- Tramadol
- Clonidine
- Baclofen
- Clonazepam

Peripheral sensitization

NE/5HT GABA

Opioid receptors

PNS
- PGEr
- Na+ TTXr
- NK-1
- VR-1
- NGF
- Opioid r
- NEr

Terminal

Spinal cord
- PGE
- Na+ TTXr
- TTXs
- TCA CBZ
- OXC TPM
- LTG
- Mexiletine
- Lidocaine

Central sensitization

Ca++:
- GBP; OXC Conotoxin

NMDA:
- Ketamine, TPM
- Dextromethorphan
- Methadone

PGE:
- NSAIDs / COX-2

Modifiers

Capsaicin

Opioids

Clonidine
REGULATIONS GOVERNING PRESCRIBING OF OPIOIDS AND BUPRENORPHINE
18VAC85-21-10. Applicability.

☐ A. This chapter shall apply to doctors of medicine, osteopathic medicine, and podiatry and to physician assistants.

☐ B. This chapter shall **not** apply to:

☐ 1. The treatment of acute or chronic pain related to (i) **cancer**, (ii) **sickle cell**, (iii) a patient in **hospice** care, or (iv) a patient in **palliative** care;

☐ 2. The treatment of acute or chronic pain during an inpatient hospital admission or in a nursing home or an assisted living facility that uses a sole source pharmacy; or

☐ 3. A patient enrolled in a clinical trial as authorized by state or federal law.
The following words and terms when used in this chapter shall have the following meanings unless the context clearly indicates otherwise:

- "Acute pain" shall mean pain that occurs within the normal course of a disease or condition or as the result of surgery for which controlled substances may be prescribed for no more than three months.
- "Board" shall mean the Virginia Board of Medicine.
- "Chronic pain" shall mean non-malignant pain that goes beyond the normal course of a disease or condition for which controlled substances may be prescribed for a period greater than three months.
- "Controlled substance" shall mean drugs listed in The Drug Control Act of the Code of Virginia in Schedules II through IV.
- "FDA" shall mean the U. S. Food and Drug Administration.
- "MME" shall mean morphine milligram equivalent.
- "Prescription Monitoring Program" shall mean the electronic system within the Department of Health Professions that monitors the dispensing of certain controlled substances.
- "SAMHSA" means the Substance Abuse and Mental Health Services Administration.
18VAC85-21-30. Evaluation of the acute pain patient

□ A. **Non-pharmacologic and non-opioid treatment** for pain shall be given consideration prior to treatment with opioids. If an opioid is considered necessary for the treatment of acute pain, the practitioner shall give a short-acting opioid in the lowest effective dose for the fewest possible days.

□ B. Prior to initiating treatment with a controlled substance containing an opioid for a complaint of acute pain, the prescriber shall perform a history and physical examination appropriate to the complaint, query the **Prescription Monitoring Program** as set forth in § 54.1-2522.1 of the Code of Virginia and conduct an assessment of the patient’s **history and risk of substance abuse**.
A. Initiation of opioid treatment for patients with acute pain shall be with short-acting opioids.

1. A prescriber providing treatment for acute pain shall not prescribe a controlled substance containing an opioid in a quantity that exceeds a seven-day supply as determined by the manufacturer’s directions for use, unless extenuating circumstances are clearly documented in the medical record. This shall also apply to prescriptions of a controlled substance containing an opioid upon discharge from an emergency department.

2. An opioid prescribed as part of treatment for a surgical procedure shall be for no more than 14 consecutive days in accordance with manufacturer’s direction and within the immediate perioperative period, unless extenuating circumstances are clearly documented in the medical record.
B. Initiation of opioid treatment for all patients shall include the following:

1. The practitioner shall carefully consider and document in the medical record the reasons to exceed 50 MME/day.

2. Prior to exceeding 120 MME/day, the practitioner shall document in the medical record the reasonable justification for such doses or refer to or consult with a pain management specialist.

3. **Naloxone shall be prescribed for any patient when risk factors of prior overdose, substance abuse, doses in excess of 120 MME/day, or concomitant benzodiazepine is present.**
C. Due to a higher risk of fatal overdose when opioids are prescribed with benzodiazepines, sedative hypnotics, carisoprodol, and tramadol, the prescriber shall only co-prescribe these substances when there are extenuating circumstances and shall document in the medical record a tapering plan to achieve the lowest possible effective doses if these medications are prescribed.

D. Buprenorphine is not indicated for acute pain in the outpatient setting, except when a prescriber who has obtained a SAMHSA waiver is treating pain in a patient whose primary diagnosis is the disease of addiction.
The medical record shall include a description of the pain, a presumptive diagnosis for the origin of the pain, an examination appropriate to the complaint, a treatment plan and the medication prescribed or administered to include the date, type, dosage, and quantity prescribed or administered.
A. Prior to initiating management of chronic pain with a controlled substance containing an opioid, a medical history and physical examination, to include a mental status examination, shall be performed and documented in the medical record, including:

1. The nature and intensity of the pain;
2. Current and past treatments for pain;
3. Underlying or coexisting diseases or conditions;
4. The effect of the pain on physical and psychological function, quality of life and activities of daily living;
5. Psychiatric, addiction and substance abuse history of the patient and any family history of addiction or substance abuse;
6. A urine drug screen or serum medication level;
7. A query the Prescription Monitoring Program as set forth in § 54.1-2522.1 of the Code of Virginia;
8. An assessment of the patient’s history and risk of substance abuse; and
9. A request for prior applicable records.
B. Prior to initiating opioid treatment for chronic pain, the practitioner shall discuss with the patient the known risks and benefits of opioid therapy and the responsibilities of the patient during treatment to include securely storing the drug and properly disposing of any unwanted or unused drugs. The practitioner shall also discuss with the patient an exit strategy for the discontinuation of opioids in the event they are not effective.
A. Non-pharmacologic and non-opioid treatment for pain shall be given consideration prior to treatment with opioids.

B. In initiating and treating with an opioid, the practitioner shall:

1. Carefully consider and document in the medical record the reasons to exceed 50 MME/day;
2. Prior to exceeding 120 MME/day, the practitioner shall document in the medical record the reasonable justification for such doses and refer to or consult with a pain management specialist.
3. Prescribe naloxone for any patient when risk factors of prior overdose, substance abuse, doses in excess of 120 MME/day, or concomitant benzodiazepine is present; and
4. Document the rationale to continue opioid therapy every three months.
C. Buprenorphine may be prescribed or administered for chronic pain in formulation and dosages that are FDA-approved for that purpose.
D. Due to a higher risk of fatal overdose when opioids, including buprenorphine, are given with other opioids, benzodiazepines, sedative hypnotics, carisoprodol, and tramadol, the prescriber shall only co-prescribe these substances when there are extenuating circumstances and shall document in the medical record a tapering plan to achieve the lowest possible effective doses of these medications if prescribed.

E. The practitioner shall regularly evaluate for opioid use disorder and shall initiate specific treatment for opioid use disorder, consult with an appropriate healthcare provider, or refer the patient for evaluation and treatment if indicated.
A. The medical record shall include a treatment plan that states measures to be used to determine progress in treatment, including but not limited to pain relief and improved physical and psychosocial function, quality of life, and daily activities.

B. The treatment plan shall include further diagnostic evaluations and other treatment modalities or rehabilitation that may be necessary depending on the etiology of the pain and the extent to which the pain is associated with physical and psychosocial impairment.

C. The prescriber shall document in the medical records the presence or absence of any indicators for medication misuse, abuse or diversion and shall take appropriate action.
18VAC85-21-90. Informed consent and agreement for treatment for chronic pain.

A. The practitioner shall document in the medical record informed consent, to include risks, benefits and alternative approaches, prior to the initiation of opioids for chronic pain.

B. There shall be a written treatment agreement, signed by the patient, in the medical record that addresses the parameters of treatment, including those behaviors which will result in referral to a higher level of care, cessation of treatment, or dismissal from care.
C. The treatment agreement shall include, but not be limited to, notice that the practitioner will query and receive reports from the Prescription Monitoring Program and permission for the practitioner to:
  1. Obtain urine drug screens or serum medication levels, when requested; and
  2. Consult with other prescribers or dispensing pharmacists for the patient.

D. **Expected outcomes shall be documented in the medical record including improvement in pain relief and function or simply in pain relief.** Limitations and side effects of chronic opioid therapy shall be documented in the medical record.
A. The practitioner shall review the course of pain treatment and any new information about the etiology of the pain and the patient’s state of health at least every three months.

B. Continuation of treatment with opioids shall be supported by documentation of continued benefit from such prescribing. If the patient’s progress is unsatisfactory, the practitioner shall assess the appropriateness of continued use of the current treatment plan and consider the use of other therapeutic modalities.

C. Practitioners shall check the Prescription Monitoring Program at least every three months after the initiation of treatment.

D. Practitioner shall order and review a urine drug screen or serum medication levels at the initiation of chronic pain management and at least every three months for the first year of treatment and at least every six months thereafter.

E. The practitioner shall regularly evaluate for opioid use disorder and shall initiate specific treatment for opioid use disorder, consult with an appropriate healthcare provider, or refer the patient for evaluation for treatment if indicated.
18VAC85-21-110. Additional consultations.

A. When necessary to achieve treatment goals, the prescriber shall refer the patient for additional evaluation and treatment.

B. When a prescriber makes the diagnosis of opioid use disorder, treatment for opioid use disorder shall be initiated or the patient shall be referred for evaluation and treatment.
The prescriber shall keep current, accurate and complete records in an accessible manner readily available for review to include:

1. The medical history and physical examination;
2. Past medical history;
3. Applicable records from prior treatment providers and/or any documentation of attempts to obtain;
4. Diagnostic, therapeutic and laboratory results;
5. Evaluations and consultations;
6. Treatment goals;
7. Discussion of risks and benefits;
8. Informed consent and agreement for treatment;
9. Treatments;
10. Medications (including date, type, dosage and quantity prescribed and refills);
11. Patient instructions; and
12. Periodic reviews.
Thank you