# *SUPPLEMENTARY MATERIAL: Fast Facts and Concepts of Pain Management*

## INTRODUCTION

The United States is facing competing crises: the need to adequately and appropriately treat acute and chronic pain and the opioid abuse epidemic. Pain—the most common complaint seen in primary care offices—affects about 20% of the country's population.[1] Untreated or undertreated pain reduces quality of life, impairs physical function, and increases costs.[2] However, addiction; unintentional overdose; and death from inappropriate prescribing, abuse, and misuse of opioids are major health care crises. Providers should reserve opioids for when non-opioid options are inadequate and opioids' benefits outweigh risks.[2] This contributes to national efforts to address and reduce opioid abuse and misuse.

## CHARACTERIZING AND ASSESSING PAIN

**Defining Pain**[1,3]

**Acute Pain**

- Sudden, intended to be a warning of disease or threat to the body (e.g., injury)
- Nociceptive (develops in response to a stimulus) peripheral nerve ending activations
- Resolves when the causal event or disease is resolved

**Chronic Pain**

- Severe pain lasting longer than 3 months
- Sufficient duration and intensity to adversely affect a patient's well-being, level of function, and quality of life
- No biological value
- Persists even if the original condition has healed or resolved

**Neuropathic Pain**

- Injury or dysfunction of the somatosensory tract of the nervous system
- Can be acute or chronic
- Patients describe burning, tingling, electrical, stabbing, or pins-and-needles

**Elements of an Initial Assessment**[2]

- Patient history
- Screening tools
    - Risk factors for developing chronic pain after acute injury[4]
        - Peripheral sensitization (reduced threshold for pain at the site of the original trauma)
        - Central sensitization (widespread reduced threshold for pain and pain due to a stimulus that normally does not provoke pain)
        - Descending modulation (altered response to the endogenous anti-nociceptive system resulting in an increased sense of pain, rather than decreased)
    - Risk factors for opioid use disorder (OUD) or abuse
- State Prescription Drug Monitoring Program (PDMP) queries
- Pain assessment scales/tools
- Functional assessment scales
- Physical examination
- Family planning (i.e., contraceptives, pregnancy intent/status, plans to breastfeed)
- Psychological and social evaluation
- Diagnostic studies when indicated

**Screening Tools and Scales for Initial Assessment of Pain[5,6,7,8]***

| | |
|---|---|
| ***Risk of OUD*** | |
| Opioid Risk Tool-OUD (ORT-OUD) | Self-administered based on personal and family history of substance abuse and presence of psychological disease |
| Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) Tool | Self- or clinician-administered; comprises 2 components:<br>• TAPS-1: 4-item screen for tobacco, alcohol, illicit drugs, and non-medical use of prescription drugs<br>• TAPS-2: If positive for TAPS-1, individual completes another assessment to assess a risk level for that substance |
| Screener and Opioid Assessment for Patients with Pain (SOAPP) | Clinician-administered to determine how much monitoring a patient on long-term opioid therapy might require |
| ***Pain assessment*** | |
| OPQRST | **O**nset of event; **P**rovocation and palliation of symptoms; **Q**uality; **R**egion and radiation; **S**everity; **T**iming |
| QISS-TAPED | **Q**uality; **I**mpact; **S**ite; **S**everity; **T**emporal characteristics; **A**ggravating and alleviating factors; **P**ast response and preferences; **E**xpectations, goals, meaning; **D**iagnostics and physical exam |
| Numerical Rating Scale (NRS) | Clinician asks the patient to make 3 pain ratings, corresponding to current, best, and worst pain experienced over the pasta 24 hours on a scale of 0 (no pain) to 10 (worst pain imaginable) |
| ***Functional assessment*** | |
| Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health | 10-item global assessment tool to evaluate physical, mental, and social health; higher score reflects better functioning |
| Work Productivity and Activity Impairment Questionnaire | 6-item, validated questionnaire to measure impairment in work and activities |
| Functional Goals | Goal-setting worksheet to assist with setting functional goals for patients with chronic pain |

*Alternative tools recommended for special populations (e.g., patients with dementia, pediatrics)
OUD = opioid use disorder

*Using State PDMPs*

PDMP is an electronic database that tracks controlled substance prescriptions in a state to deliver timely information to health care providers.[9] State requirements vary regarding who must register with the PDMP and when they must use it. States may require that[10]

- all prescribers must register or certain prescribers must register (e.g., pain management practitioners, those prescribing controlled substances)
- both prescribers and dispensers must register
- prescribers and dispensers must actively use the PDMP
- prescribers must use the PDMP only under certain circumstances (e.g., when they suspect abuse/misuse)

Ideally, prescribers always check the PDMP before prescribing, but pharmacists should also use the database before dispensing opioid prescriptions to identify and address patient safety issues (e.g., drug interactions, potential misuse/abuse, overdose potential), and public health risks (e.g., pill mills).

## TREATING PAIN

**Components of an Effective Treatment Plan[2]**

- Goals of treatment
  - Degree of improvement in pain (and function if function has been impaired by pain)
- Constituents of the treatment plan (nonpharmacologic and pharmacologic)
- Patient/prescriber/health care team interactions
  - Patient responsibilities/compliance with the plan
  - Prescriber and health care team responsibilities
  - Plans for reviewing functional goals
  - Directions for supplemental medication use for intermittent increases in pain
  - Use of patient-prescriber agreements (PPAs)

*Patient-Prescriber Agreements*

Opioid PPAs are designed to[11]

- create an open conversation between the patient and the prescriber about benefits, risks, and limitations of opioid medications
- act as decision-making tools before prescribing opioid medications for acute or persistent pain
- encourage the appropriate and safe use of opioid medications

Parts of an opioid PPA include, but are not limited to[11]

- Deciding whether to use opioid medications for pain
  - Treatment expectations, potential adverse effects (e.g., physical dependence, tolerance, addiction), and drug interactions
- Pledging to prescribe and use opioid medications safely
  - Full patient disclosure of all other medications (prescription, over-the-counter, and herbal)
  - Safe storage and disposal instructions and pledge not to share opioids with others
  - Prescriber agreement not to "cold discharge" a patient from practice without appropriate transition of care to another provider

**Nonpharmacologic Therapies for Pain Management[12,13,14,15,16]**

| Therapy Type | When It Should Be Used | How it Works |
|---|---|---|
| Psychological (e.g., cognitive behavioral therapy) | Adjunct to other therapies for chronic pain | Addresses the psychological consequences of pain, including depression, anxiety, posttraumatic stress, negative quality of life, increased disability, sleep disturbance, and fatigue |
| Physical rehabilitation (e.g., exercise therapy, massage, electrical stimulation) | Acute or chronic pain | Movement-based pain relief based on the belief that all forces in the body affect each other |
| Surgical (e.g., nerve repair) | Pain unresolved by other methods lasting 3 months (e.g., following prior surgery or trauma) | Depends on location and cause; often involves relieving pressure from an affected nerve |
| Complementary and alternative therapies (e.g., herbs, acupuncture, meditation) | Acute or chronic pain after careful consideration of risks/benefits | Variable; herbs are often anti-inflammatory or work via desensitization (low evidence); acupuncture may increase regional blood flow and endogenous opioid release (moderate evidence); mind-body therapies |

| | | |
|---|---|---|
| | | like meditation or hypnosis may reduce stress to decrease pain perception (moderate evidence) |
| Transcutaneous electrical nerve stimulation (TENS) | Chronic nociceptive or neuropathic pain | A small electricity-generating device connected via flexible cables to 1 or more pairs of patch electrodes; causes release of endorphins and their precursors |

**Non-Opioid Analgesic Medications*[17]**

| Drug | Dosing | Indications | AEs and Risks | Other Information |
|---|---|---|---|---|
| **Acetaminophen** | 650 mg every 4-6 hours (max 4 g/day) | Mild-to-moderate pain | CI in severe hepatic impairment or severe active liver disease | Not effective for neuropathic pain |
| **Aspirin** | 350-650 mg every 4 hours (max 3600 mg/day) | Mild pain (temporary use), inflammatory rheumatic diseases | Nausea, dyspepsia, abdominal pain, bleeding tendency, tinnitus, headache, dizziness, insomnia; risk of GI bleeding | Not effective for neuropathic pain |
| **NSAIDs** *Aspirin, celecoxib, diclofenac, etodolac, ibuprofen, ketoprofen, ketorolac, naproxen* | Depends on the specific drug | Mild-to-moderate pain; pain associated with inflammation | Nausea, dyspepsia, diarrhea, constipation, headache, dizziness, somnolence; risks of GI bleeding, MI, stroke | Not effective for neuropathic pain; lowest effective dose for the shortest period |
| **Amitriptyline** | 25-150 mg once daily or in 2 divided doses (max 75 mg/dose) | Neuropathic pain (first-line), fibromyalgia, prevention of tension-type headache or migraine | Somnolence, tremor, dizziness, headache, drowsiness, tachycardia, orthostatic hypotension, dry mouth, constipation, nausea, weight gain, hyperhidrosis; increased risk of suicidal thoughts | Use lower doses in poor CYP2D6 metabolizers; avoid abrupt d/c; CI with recent MI or cardiac rhythm disorders; caution with other serotonergic agents |
| **Duloxetine** | 60-120 mg once daily or in 2 divided doses | Neuropathic pain (first-line), chronic musculoskeletal pain, fibromyalgia | Nausea, headache, dry mouth, somnolence, dizziness, increased blood pressure; increased risk of suicidal thoughts | Avoid abrupt discontinuation; caution with other serotonergic agents |
| **Gabapentin** | 900-3600 mg/day in 3 divided doses | First-line therapy for neuropathic pain | Dizziness, somnolence, peripheral edema, fever, infection, nausea, lack of coordination, blurred vision; increased risk of suicidal thoughts | Dose adjustment required for decreased renal function; misuse, abuse, or dependence possible |
| **Pregabalin** | 300-600 mg/day in 2 divided doses | Neuropathic pain (first-line), fibromyalgia | Dizziness, somnolence, headache, peripheral edema, nausea, weight gain, disorientation, blurred vision; increased risk of suicidal thoughts | Dose adjustment required for decreased renal function; misuse, abuse, or dependence possible |
| **Lidocaine** *1.8% or 5% patch* | 1-3 patches applied to intact skin for up to 12 hours/day | Peripheral neuropathic pain | Application-site pain, pruritis, erythema, skin irritation | FDA-approved for postherpetic neuralgia only |

*Drugs listed are those commonly used, but this list is not all-inclusive for every pain indication; all dosing provided is oral.
CI, contraindicated; COX, cyclooxygenase; d/c, discontinuation; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug

*Acetaminophen:* Analgesic and fever-reducing effects are well-known, but mechanism of action is not. When used around-the-clock/scheduled, it has been shown to be opioid-sparing.
*Aspirin and other NSAIDs:* Alleviate pain and reduce fever and inflammation by decreasing the synthesis and release of prostaglandins. Cyclooxygenase-2 (COX-2) inhibitors also inhibit prostaglandin synthesis and release, but unlike aspirin and non-selective NSAIDs, COX-2 inhibitors do not inhibit platelet aggregation. When used around-the-clock/scheduled, it has been shown to be opioid-sparing.
*Antidepressants:* Tricyclic antidepressants (TCAs; amitriptyline) and serotonin-norepinephrine reuptake inhibitors (SNRIs; duloxetine) have unknown mechanisms for their pain-relieving properties. May be related to presynaptic inhibition of serotonin and norepinephrine reuptake in pain inhibitory pathways, as well as a peripheral mechanism involving β2-adrenergic receptors.
*Anticonvulsants:* (e.g., gabapentin, pregabalin) Provide analgesia by lowering neurotransmitter release or reducing neuronal firing by binding to voltage-gated calcium channels in the central nervous system (CNS).
*Topical treatments:* Topical non-opioid medications (e.g., lidocaine) act locally. Lidocaine works by blocking nerve signals that send the feeling of pain from the site of injury to the brain. It causes a temporary loss of feeling in the area to which it is applied.

**Opioid Analgesic Medications**
*Full agonists* bind to the opioid receptors and undergo significant conformational change to produce maximal effect.[18]

- EXAMPLES: codeine, fentanyl, hydrocodone, methadone, morphine, oxycodone

*Partial agonists* cause less conformational change and receptor activation than full agonists. When dose increases, analgesic activity will plateau and further increases will potentiate adverse effects without providing additional pain relief.[18]

- EXAMPLES: buprenorphine, tramadol

*Extended release (ER)* or *long acting (LA):* delivers drug in a controlled manner during an extended period of time following administration
*Immediate release (IR):* developed to dissolve without delaying or prolonging dissolution or absorption of the drug

*Abuse-Deterrent Formulations (ADFs):* possess properties meant to meaningfully deter abuse (e.g., crushing, snorting, smoking, dissolving, injecting), even if they do not fully prevent abuse (NOT "tamper-resistant")[19]

- Examples: physical/chemical barriers to prevent changing the drug's physical dosage form, agonist/antagonist combinations, aversion (i.e., adding an unpleasant substance that releases when manipulated)
- All ADFs have the same potential for addiction and overdose death as non-ADFs

*Contraindications and Precautions*

- Opiate allergies within the same class
    - See https://paindr.com/wp-content/uploads/2020/11/Opioid-Structural-Classes-Figure_-updated-2020Nov.pdf for cross-sensitivity risk
- Pulmonary diseases (asthma, COPD)

- Head injuries, increased intracranial pressure
- Sleep apnea
- Short gut syndromes (e.g., ulcerative colitis)

*Significant Drug Interactions*[20]

- CNS depressants (e.g., alcohol, sedatives, hypnotics, tranquilizers, TCAs) can potentiate opioid-induced sedation and respiratory depression
- Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. Some drug levels may increase without dose dumping when exposed to alcohol. See individual product labeling.
- Using opioids with monoamine oxidase inhibitors (MAOIs) may potentiate respiratory depression. Using certain opioids with MAOIs may cause serotonin syndrome.
- Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone (ADH).
- Some opioids (e.g., methadone, buprenorphine) can prolong the QTc interval.
- Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids.

*Commonly-Used Opioid Analgesics (Outpatient)*[21,22,23]

| Opioid | Route(s) of Administration | Usual Starting Dose[a] |
|---|---|---|
| Buprenorphine[b] | transdermal patch | 5 mcg/hr patch applied every 7 days |
| Fentanyl | transdermal patch<br><br>buccal tablets | 25 mcg/hr patch applied every 3 days<br><br>100 mcg every 4 hours as needed |
| Hydrocodone ER | oral | 8 mg once daily |
| Hydromorphone | oral | 2 mg every 4-6 hours |
| Methadone[b] | oral | 2.5 mg 3 times daily |
| Morphine | oral | 10 mg every 4-6 hours |
| Morphine ER capsule | oral | 20 mg every 12 or 24 hours |
| Morphine ER tablet | oral | 15–30 mg every 8–12 hours |
| Oxycodone | oral | 5 mg every 4-6 hours |
| Oxycodone ER | oral | 10 mg every 12 hours |
| Oxymorphone | oral | 5mg every 4-6 hours |
| Oxymorphone ER | oral | 5 mg every 12 hours |
| Tapentadol ER | oral | 50 mg every 12 hours |
| Tramadol ER | oral | 25 mg once daily |

[a]May be lower in patients with renal failure, hepatic failure, or age > 65 years, see full prescribing information at https://www.accessdata.fda.gov/scripts/cder/daf/.

[b]Also used for OUD. No prescribing restrictions for methadone when using to treat pain and no XDEA licensing required when using buprenorphine to treat pain.

ER, extended-release

*General Safety Notes*

- Even at prescribed doses, opioid analgesics carry the risk of misuse, abuse, OUD, overdose, and death
    - Risk of significant respiratory depression is greatest at treatment initiation, with dose increases, and upon addition of any other CNS depressants
    - Interindividual variability in response to opioids results from[24]
        - Genetics (e.g., mu receptors encoded by the OPRM1 gene)
        - Pharmacokinetics (e.g., hepatic metabolism)
        - Subjectivity of pain and the pain experience
- Use PDMPs appropriately as a clinical decision support tool when dispensing opioid medications
- Patients receiving 60 mg oral morphine milliequivalents (MME) daily for ≥ 1 week are considered opioid-tolerant[20]
    - Conversion factor charts like the one shown here are helpful for determining MME of patients' current opioid dosing, but health care providers should not rely on them for safe conversion between products (discussed further below)

| Opioid (mg/day unless noted) | Conversion Factor |
|---|---|
| **Codeine** | 0.15 |
| **Fentanyl transdermal** (mcg/hr) | 2.4 |
| **Hydrocodone** | 1 |
| **Hydromorphone** | 4 |
| **Morphine** | 1 |
| **Oxycodone** | 1.5 |
| **Oxymorphone** | 3 |

- Some opioid analgesics are FDA approved only for opioid-tolerant patients[20]
    - Transmucosal IR fentanyl products
    - Transdermal fentanyl
    - ER hydromorphone
    - Specific doses of other ER/LA products (see full prescribing information)
- Medication errors[25]
    - 2000 through 2012, U.S. poison control centers received 533,763 calls about unintentional analgesic medication errors, averaging 41,059 medication errors annually or one error every 13 minutes
        - 23.2% involved opioids
        - 42.1% of resultant deaths involved opioids

*Key Safety Strategies*[2]

- Provide clear dosing instructions including daily maximum
- Emphasize safe storage to reduce risk of accidental exposure/ingestion by household contacts, especially children/teens, and to reduce risk of theft
- Encourage naloxone products for use in the home to reduce risk of overdose deaths in patients and household contacts
- Stress proper disposal of used (e.g., transdermal systems) and unused opioids
- Discuss pain management after an opioid overdose
- Counsel on driving and work safety

*Opioid Use in Special Populations*

- Pregnant, postpartum/breastfeeding[26]
    - Associated with stillbirth, poor fetal growth, pre-term delivery, and birth defects
        - Neonatal opioid withdrawal syndrome: infants with in-utero opioid exposure may exhibit withdrawal symptoms after birth, including GI dysfunction (loose

stools, vomiting), autonomic dysfunction (temperature dysregulation, sneezing), and neurologic signs of irritability and tremors[27]
    - Taking opioids while breastfeeding may cause neonatal somnolence
        - Neonatal toxicity and death have been reported in breastfeeding infants whose mothers are taking codeine
- Renal and hepatic impairment[26]
    - Decreased ability to process and excrete drugs, susceptibility to opioid accumulation, and reduced therapeutic window between safe dosages and dosages associated with respiratory depression, neurotoxicity, and overdose
- Children and adolescents[28]
    - Fentanyl, morphine, and methadone are used in all ages, including neonates
    - Oxycodone and hydromorphone are FDA approved for those > 6 months of age
    - Hydrocodone is commonly used off-label for patients < 2 years old
    - FDA issued a Boxed Warning for codeine and tramadol in children < 12 years old
- Genetic and phenotypic variations[29]
    - CYP3A4 and CYP2D6 are primarily responsible for opioid metabolism
    - Patients can possess varying phenotypes of CYP2D6 making them ultrarapid, extensive, intermediate, or poor metabolizers
- Older adults[26]
    - Inadequate pain management among persons aged ≥ 65 years is common
    - Reduced renal function and medication clearance even in the absence of renal disease
    - Cognitive impairment can increase risk for medication errors and make opioid-related confusion more dangerous
    - Increased prevalence of comorbidities, so increased risk of drug-drug interactions
- Sleep-disordered breathing[26]
    - Mild: careful monitoring and dose titration
    - Moderate or severe: avoid opioids to minimize overdose risk
- Mental health conditions[26]
    - Psychological distress frequently interferes with improvement of pain and function in patients with chronic pain
    - Do not initiate opioid therapy during acute psychiatric instability or uncontrolled suicide risk
    - Patients are more likely to be on benzodiazepines
    - Consider pain relieving effects of TCAs or SNRIs

## MANAGING PATIENTS ON OPIOID ANALGESICS

*Much of treatment initiation falls to prescribers, but the basics for pharmacists are outlined below.*

**Considerations for Treatment Initiation: Acute[2,26]**

1) Patient selection
    a. Consider when an opioid is appropriate
        i. NSAIDs associated with similar or greater improvements in pain and function than opioids
    b. Consult the PDMP
        i. Other prescriptions (other opioids, benzodiazepines, etc.)
        ii. High total dosages
2) Dosing
    a. Start with short-acting opioids only

i. Initiation with ER/LA opioids is associated with increased overdose risk[26]
ii. Consider appropriateness of as-needed versus around-the-clock dosing

b. Prescribing an appropriate quantity based on the expected duration of pain
i. Least amount necessary and for the shortest duration (3 days often sufficient, > 7 days rarely needed); encourage quick follow up if pain persists

3) Naloxone for home use
a. Prescribe and discuss the use of naloxone products and the various means of administration

4) Screening tools for risk of abuse
a. ORT-OUD
b. TAPS
c. SOAPP

**Naloxone Products for Home Use[30,31,32]**

| | Narcan | Kloxxado | Zimhi |
|---|---|---|---|
| **Route** | Nasal | Nasal | Intramuscular/Subcutaneous |
| **Dose** | 4 mg/0.1 mL | 8 mg/0.1 mL | 5 mg/0.5 mL |
| **Administration** | 1) Call 911 and lay person on their back<br>2) Remove from the box and peel back the tab<br>3) Hold with your thumb on the bottom of the red plunger and your first and middle fingers on either side of the nozzle<br>4) Tilt the person's head back and support under their neck with your hand<br>5) Gently insert the tip of the nozzle into 1 nostril until your first and middle fingers are against the bottom of the nose<br>6) Firmly press the plunger, then remove the device from the nose after the dose is delivered<br>7) Roll the person to their side to wait for help<br>8) If additional doses are available, repeat steps 2-6 every 2-3 minutes until the person response or help arrives | | 1) Call 911 and lay person on their back<br>2) Pull off cap to expose needle, do not put a finger on top of the device<br>3) Hold by the finger grips and slowly insert the needle into the thigh<br>4) After needle is all the way in, push the plunger all the way down until it clicks and hold for 2 seconds<br>5) Using 1 hand with fingers behind the needle, slide the safety guard over the needle<br>6) Put the used syringe into the blue case and close the case<br>7) Roll the person to their side to wait for help<br>8) If symptoms continue or return, dose may be repeated with a new syringe every 2-3 minutes |
| **Clinical Pearls** | • No age minimum<br>• Do not remove from package until ready to use<br>• Each nasal spray has 1 dose; cannot be reused<br>• Does not need to be primed<br>• Freezes at < 5°F and will not spray; can still be used if thawed after previously frozen | | • Intended to be administered by people ≥ 12 years old<br>• If person is < 1 year old, pinch the thigh muscle while administering<br>• Each injector has 1 dose; cannot be reused<br>• It is normal for medicine to remain in the syringe after injection; the correct dose has been injected if the plunger is fully depressed and the solution window is at least partially blocked |

**Considerations for Treatment Initiation: Chronic[2,26]**

1) Patient selection
    a. Differences in benefits, risks, and expected outcomes for patients with chronic pain, palliative care, or end-of-life care
        i. Opioids should not be considered first-line or routine therapy for chronic pain outside of active cancer, palliative, and end-of-life care, given small to moderate short-term benefits, uncertain long-term benefits, and potential for serious harms
    b. Opioid-naive versus opioid-tolerant patients
        i. See product limitations above
2) Dosing
    a. As-needed versus around-the-clock
    b. Determining a safe initial dose
        i. Start low and titrate slow
    c. Safe conversion from other opioids using a validated equianalgesic dosing table
3) Opioid selection
    a. IR or ER/LA
        i. Prescribers should only use ER/LA opioid formulations in opioid-tolerant patients who have achieved adequate pain control with immediate-release opioid formulations
    b. Special precautions with methadone
        i. Subject to more interindividual variability than other opioids
    c. Products restricted to opioid-tolerant patients
4) Opioid or non-opioid analgesics to supplement pain management

**Ongoing & Long-Term Management[2,26]**

1) Periodic review of pain and functional goals
    a. Evaluate benefits and harms within 1-4 weeks of starting therapy or of dose escalation
    b. Evaluate for changes in underlying condition or signs of OUD before increasing dose for worsening pain
    c. Carefully reassess benefits and risks when considering increasing dosage to ≥ 50 MME/day
        i. Avoid increasing dosage to ≥ 90 MME/day
2) Review adverse events at each visit
    a. Eliciting signs or symptoms of abuse
    b. Screening for endocrine function
        i. Long-term opioid use is associated with increased risk for erectile dysfunction treatment or testosterone replacement
3) Review refill history/PDMP
    a. With each prescription or at least every 3 months
4) Referral to a pain specialist
    a. Patients high risk for OUD
    b. Patients unable to achieve adequate pain management
5) Determining when an opioid is no longer necessary/beneficial
    a. Evaluate benefits and harms of continued therapy at least every 3 months

*Changing Opioid Medications*[33,34]

- Conversion between opioid products must take into account many drug- and patient-specific factors that impact safety, including (but not limited to)
    - Morphine is metabolized to toxic metabolites that accumulate in patients with renal dysfunction
    - Codeine is a pro-drug metabolized to morphine in the liver
    - Tapentadol has an additional mechanism of action as a norepinephrine reuptake inhibitor
    - Tramadol is a pro-drug requiring activation by the liver via CYP3A4 and CYP2D6, has additional mechanisms of action including serotonin and norepinephrine reuptake inhibition, and may lower seizure threshold
- Equianalgesic dosing charts like the one pictured below are NOT representative of dosing for individual patients; they are based on limited available equivalency data
    - Decrease dose by 25% to 50% to account for <u>incomplete cross-tolerance</u> or individual variations in opioid pharmacokinetics when converting between opioid drug products, but NOT when converting between routes of administration of the same drug (e.g., IV morphine to oral morphine)
    - Some express fentanyl dosing in mg, but in clinical practice fentanyl is dosed in mcg (caution when converting)
        - IV to transdermal fentanyl is approximately 1:1
- Additional reputable resource for opioid conversion based on validated data: https://opioidcalculator.practicalpainmanagement.com/

**Equianalgesic Dosing of Opioids**[34] *(see disclaimer above)*

| Drug | Parenteral (mg) | Oral (mg) |
|---|---|---|
| **Codeine** | 100 | 200 |
| **Fentanyl** | 0.15 | --- |
| **Hydrocodone** | --- | 25 |
| **Hydromorphone** | 2 | 5 |
| **Morphine** | 10 | 25 |
| **Oxycodone** | --- | 20 |
| **Oxymorphone** | 1 | 10 |
| **Tapentadol** | --- | 100 |
| **Tramadol** | --- | 120 |

*Monitoring Adherence to the Treatment Plan*[26]

1) Medication reconciliation
    a. Recognize, document, and address aberrant drug-related behavior
    b. Use non-judgmental language but be direct in identifying concerns
2) Determine if nonadherence is due to inadequate pain management
3) Urine drug testing
    a. Before starting opioid therapy and at least annually, or more frequently if new aberrant behaviors present
    b. Assess for prescribed medications and other controlled prescription or illicit drugs
4) Screen and refer for substance use disorder (SUD) treatment when concerns arise

a. Many patients can have SUD/OUD and concomitant pain conditions, both of which require evidence-based treatment

*Treatment Discontinuation*[35]

- Medically-directed opioid tapering
  - Slowest taper (over years): reduce by 2% to 10% every 4 to 8 weeks
    - Consider for patients taking high doses of ER/LA opioids for many years
  - Slower taper (over months or years): reduce by 5% to 20% every 4 weeks
    - Most common taper
  - Faster taper (over weeks): reduce by 10% to 20% every week
    - Can cause withdrawal
  - Rapid taper (over days): reduce by 20% to 50% of first dose if needed, then reduce by 10% to 20% every day
    - May be required in certain circumstances (e.g., drug diversion, illegal activities, or situations where risks of continuing the opioid outweigh those of a rapid taper)
    - If due to concerns for OUD, appropriate treatment referrals are preferred over rapid taper
    - Likely to cause withdrawal; consider admitting for inpatient care
- Withdrawal symptoms
  - Early (hours to days): anxiety/restlessness, rapid short respirations, runny nose, tearing eyes, sweating, insomnia, dilated reactive pupils
  - Late (days to weeks): runny nose, tearing eyes, rapid breathing, yawning, tremor, diffuse muscle spasms/aches, piloerection, nausea/vomiting/diarrhea, abdominal pain, fever/chills
  - Prolonged (weeks to months): irritability, fatigue, bradycardia, decreased body temperature, craving, insomnia
  - Monitor and treat using the Clinical Opiate Withdrawal Scale (COWS; Available at: https://nida.nih.gov/sites/default/files/ClinicalOpiateWithdrawalScale.pdf) and appropriate supportive therapy
- Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor

**Recognize and Intervene for Suspected or Identified OUD**[36,37]

***S**creening, **B**rief **I**ntervention, and **R**eferral to **T**reatment (SBIRT):*

- Screening – quickly assess the severity of substance use and identify the appropriate level of treatment
  - Red flags that might indicate OUD include
    - Use of many pharmacies or doctors
    - Prescriptions from providers outside of their scope of practice
    - Prescriptions for unusual quantities or combinations of medications or very high dosages
    - Presents to the pharmacy intoxicated
    - Pays in cash/will not use insurance coverage
    - Demands certain brands of medication
    - Requests frequent early refills

        - Fills only the controlled substance even though accompanied by other prescriptions
        - Makes frequent trips to the ER for pain medications
        - Frequently travels a long distance to obtain
- Brief intervention – focus on increasing insight and awareness regarding substance use and motivation toward behavioral change
    - Best practices for talking to patients about SUDs
        - Choose a quiet, private location to discuss patient history or treatment response
        - Use open-ended questions that require more than yes/no answers
        - Employ person first language and avoid stigmatizing/judging words
        - Ask about alcohol or substance use to obtain a complete medication history and make clinical recommendations. Collecting this information should be considered routine practice
        - Encourage patients to use the same pharmacy for all prescriptions
        - Get to know local community pharmacists to develop rapport and coordinate patient care concerns
        - Keep in mind that drug-seeking behavior is generally indicative of untreated SUD
        - Do not make clinical decisions based on staff hearsay
        - Do not avoid or refuse to fill without discussion to clarify concerns as this does not resolve potential diversion and can deny a patient access to a necessary medication
- Referral to treatment – provide those identified as needing more extensive treatment with access to specialty care
    - Develop a local resource list
        - Pharmacists are much more likely to intervene if resources have already been identified and are readily available
        - Patients can also be referred to their primary care physicians, employee assistance programs, self-help groups, and/or health insurance companies
    - Substance Abuse and Mental Health Services Administration (SAMHSA) also offers helpful resources
        - Behavioral health treatment services locator (includes SUD treatment): 1-800-662-HELP, https://findtreatment.samhsa.gov/
        - Buprenorphine treatment physician locator: http://www.samhsa.gov/medication-assisted-treatment/physician-programdata/treatment-physician-locator/
        - Opioid treatment program directory: http://dpt2.samhsa.gov/treatment/directory.aspx

**Patient Education and Counseling[2]**

Pharmacists should counsel patients initiating opioid treatment on the following:

- Importance of adherence to prescribed dosing regimen
- Prevention and management of opioid-induced constipation (OIC); stimulant laxatives only
- Using the least amount of medication necessary to treat pain and for the shortest duration
- The risk of serious adverse events that can lead to death
- The risk of addiction that can occur even when product is used as recommended

- Known risk factors for serious adverse events, including signs and symptoms of overdose and opioid-induced respiratory depression, GI obstruction, and allergic reactions, among others
- The most common adverse effects, along with the risk of falls, working with heavy machinery, and driving
- When to call the prescriber (e.g., managing adverse events, ongoing pain)
- How to handle missed doses
- The importance of full disclosure of all medications and supplements to all health care providers and the risks associated with the use of alcohol and other opioids/benzodiazepines
- Product-specific concerns (e.g., do not crush or chew ER products; do not cut, tear, or damage transdermal systems and buccal films before use)
- How to safely taper dose to avoid withdrawal symptoms
- Safe storage and disposal, risks of theft by family members and household visitors
- Never share any opioid analgesic with another person
- How and when to use naloxone products and their various means of administration
- Seeking emergency medical treatment if an opioid overdose occurs
- How to report adverse events and medication errors to FDA (1-800-FDA-1088 or via http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf)

Use the Opioid Analgesic REMS *Patient Counseling Guide: What You Need to Know About Opioid Pain Medicines* as part of the discussion with patients and caregivers.
https://opioidanalgesicrems.com/Resources/Docs/patient_counseling_document.pdf

## ADDICTION MEDICINE PRIMER

- Avoid stigmatizing or blaming language
- Use language that acknowledges that addiction (reclassified as *substance use disorder* in the revised Diagnostic Statistical Manual-V [DSM-5]) is a disease[38]
    - Say “substance use disorder”
    - Avoid the words “drug habit”, which implies a choice to use substances (and thus that stopping is a choice, or “problem”
    - Use person-first language (person with a SUD, person with an OUD, person with an alcohol use disorder)
    - Avoid the dehumanizing words “addict”, “junkie”, or “user”; conversely, avoid referring to patients in recovery as “clean”
    - Say “drug use” or “unhealthy use” if referring to prescription medications, not “drug abuse”
    - Do not refer to urine drug screen results as “clean” or “dirty”; instead use descriptors such as “positive for” or “negative for”
- Use the term *opioid use disorder (OUD)* when referring to the use of opioids, rather than other substances

**Screening Tools to Identify Patients at Risk of Developing OUD**

| Tool | Description | Link |
|---|---|---|
| **The NIDA Drug Use Screening Tool: Quick Screen** | Includes multiple tools for various substance use disorders | https://nida.nih.gov/nidamed-medical-health-professionals/screening-tools-resources/chart-screening-tools |
| **Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) Tool** | A combined screening component (TAPS-1) followed by a brief assessment (TAPS-2) for those who screen positive | https://nida.nih.gov/taps2/ |
| **Brief Screener for Tobacco, Alcohol, and other Drugs (BSTAD)** | Screening tool for identifying problematic tobacco, alcohol, and marijuana use in adolescents | https://nida.nih.gov/bstad/ |
| **Current Opioid Misuse Measure (COMM)** | A 9-item self-assessment to detect problematic opioid - related behavior in patients with pain who are receiving opioid therapy | https://www.painedu.org/opioid-risk-management-2/ |

**Defining Addiction[22,39]**

- DSM-5 (R) criteria for OUD differentiates abuse (taking an opioid to get high) vs. misuse (taking more than prescribed for pain or giving to someone else in pain)
- Tolerance and physiological dependence differ from OUD or SUD
    - Tolerance is the physiologic adaptation resulting in decreased efficacy of a medication/dose over time and the need for progressively higher opioid doses to obtain the same analgesic effect
        - Tolerance may cause a decrease in pleasurable effects and may be a risk factor for OUD
        - All patients on long-term opioid therapy will develop tolerance and physical dependence, even when OUD is not present
    - On a molecular level, tolerance is thought to develop as a result of desensitization of the mu opioid receptors leading to alterations in opioid receptor signaling.
    - Dependence is a physiological and follows progressive adaptation of mu opioid receptors and their cellular mechanisms to opioid medications
        - Dependence leads to withdrawal symptoms once medication is abruptly discontinued
        - Opioid dependence is almost ubiquitous with chronic opioid use but does not necessarily lead to OUD

**Neurobiology of OUD (Addictive Cycle)[40]**

*Drugs of abuse affect a variety of neuronal circuits.*

- Impact the processing of rewarding and aversive stimuli, interoception (sensitivity to stimuli originating inside of the body), emotions, decision-making, and cognitive control
- Subsequently, drug use becomes an automatic, compulsive behavior
- Changes in synaptic connections can persist long after a drug has cleared the system

*Addiction probably has components of impulse control disorders and compulsive disorders.*

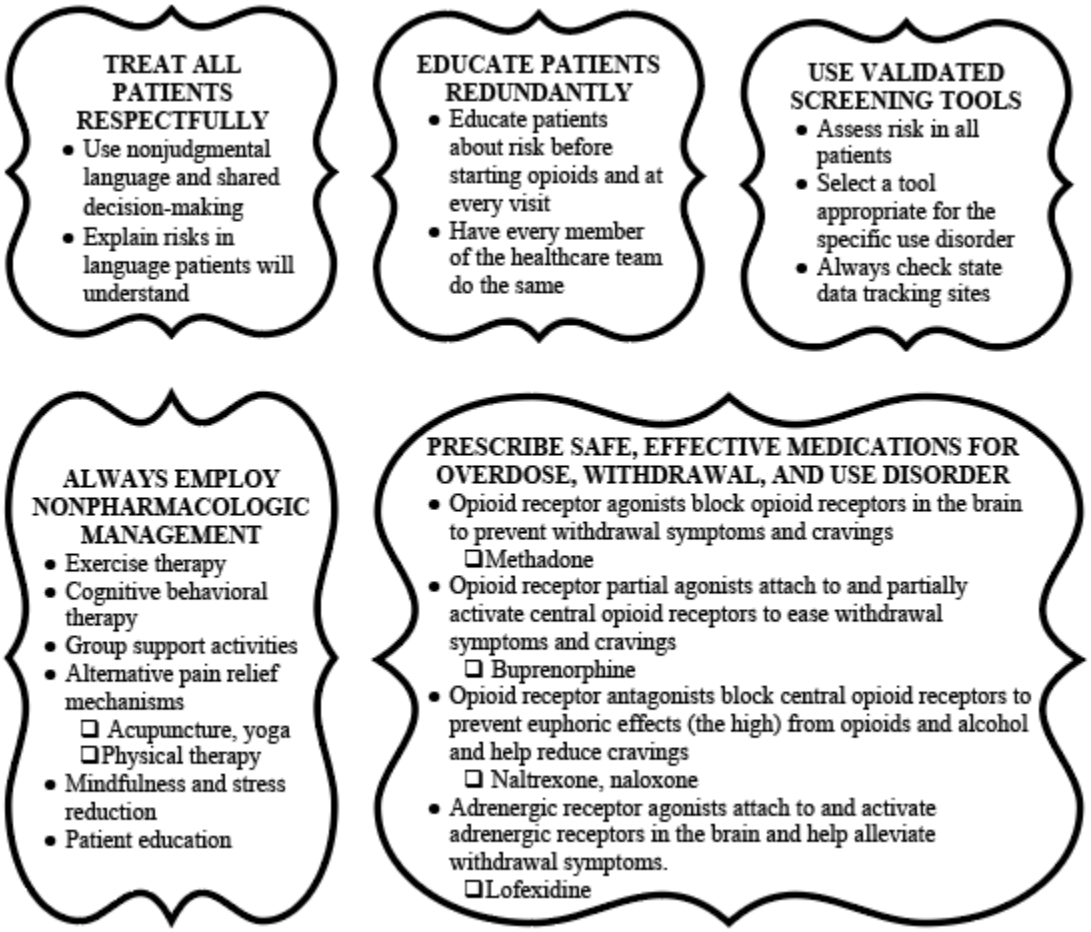
- Increasing tension or arousal before committing an impulsive act is followed by an added sense of pleasure, gratification or relief during the act
    - Positive reinforcement occurs when drugs produce pleasurable effects, increasing the likelihood that the individual will seek and use drugs again
    - Impulsive behavior's function is to produce gratification or pleasure
- Similarly, the compulsive component has increasing anxiety and stress before committing a compulsive and repetitive behavior followed by relief
    - Negative reinforcement eliminates the unpleasant stimulus and increases the likelihood of a specific response, so if taking a drug provides relief of withdrawal or other negative emotional states, the individual will repeat the behavior
    - Compulsive behavior's function is to produce relief (not pleasure) by reducing negative or painful affects

*Thus, substance use disorders seem to impair motivation-reward systems, affect regulation, and behavioral inhibition.*

- An impaired motivation-reward reinforces rewards and associated behaviors
- Impaired affect regulation increases vulnerability to discomfort from stress and emotional instability and strongly reinforces behaviors that offer relief from these feelings
- Impaired behavioral inhibition reduces the ability to delay gratification; short-term relief or gratification will frequently trump possible long-term consequences

*Collectively, these effects make resisting behaviors associated with reward system activation and relief from negative affect extremely hard to resist.*

**Management of OUD**



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