Opioid Therapy IS Associated with Abuse and Misuse: Tips to Manage Such in Your Practice

Learning Objectives

1. Apply strategies to elevate patients receiving opioids in follow up visits
2. Review best practices to manage patients suspected of opioid abuse
3. Outline methods to combat opioid abuse and comply with regulations related to opioid abuse

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Definitions: Misuse and Abuse

- **Misuse**: Intentional or unintentional use of medication for medical purpose other than as directed.
- **Abuse**: Use of illegal drug or intentional self-administration of medication for nonmedical purpose.

American College of Preventive Medicine.

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Definitions associated with opioid use

- **Addiction**: Primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. May be characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.
- **Pseudoaddiction**: Syndrome resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior. Behavior ceases when adequate pain relief is provided. Not a diagnostic; rather, a description of a clinical interaction.
- **Physical dependence**: State of adaptation manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and administration of an antagonist.
- **Tolerance**: State of adaptation in which exposure to a given drug dose induces biologic change resulting in diminution of one or more of the drug’s effects over time. Alternatively, escalating doses of a drug are required over time to maintain a given level of effect.

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The number of pain medication prescriptions correlates well with the prevalence of chronic pain

![Graph showing the prevalence of chronic pain](http://www.acpm.org/?UseAbuseRxClinRef#Prevalence)

- More than the other serious diseases listed combined

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Opioid harm is not limited to non-medical users: the Opioid Continuum

- Misuse can include use with other CNS depressant drugs, dosing errors, or use for non-pain-related purposes (ie, abuse)

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The U.S. opioid overdose epidemic – a top public health challenge

- Use of opioid analgesics has increased steadily from 2000 through 2012¹
- Trend driven by expanded use of opioid analgesics for chronic non-cancer pain
- During the same time frame, overdose deaths involving opioid analgesics have nearly quadrupled²
- 207 million prescriptions for the three most commonly prescribed opioid analgesics were dispensed in US pharmacies in 2013³

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Pain Management Goal: Define most appropriate treatment regimen for each person in pain, which could include opioids

![Diagram showing pain management strategies](http://www.acpm.org/?UseAbuseRxClinRef#Prevalence)

- Pharmacotheraphy
- Physical medicine and rehabilitation
- Psychological support
- Complementary and alternative medicine
- Lifestyle change
- Pain intervention strategies for pain and associated disability
- Psychological support
- Pharmacotheraphy

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³Passik SE, et al. Palliative Care and Supportive Oncology. 2002

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Rational use of opioid analgesics for chronic cancer and non-cancer pain

- Dichotomy of “pro-opioid” and “anti-opioid” is false, and does not serve healthcare professionals, patients, or society well
  - Ethical healthcare providers are “pro-health” and make treatment decisions within that context
- Clinicians must
  - Learn how to select patients for opioid therapy, when indicated
  - Manage patients on opioid therapy as safely and effectively as possible

Opioid Receptors

- Administered opioids bind to the same three receptor subtypes that normally bind endogenous opioid peptides:
  - µ (MOP): Analgesia, sedation, respiratory depression, bradycardia, nausea, vomiting, reduced gastric motility
  - δ (DOP): Spinal/supraspinal analgesia, reduced gastric motility
  - κ (KOP): Spinal analgesia, diuresis, dysphoria
- Opioids can be classified according to their effect at opioid receptors:
  - Agonists: act at a receptor to produce maximal receptor-mediated responses; eg, morphine and analgesia
  - Antagonists: bind to a receptor but do not cause a functional response; binding prevents an agonist from binding to that receptor, however, eg, naloxone
  - Partial agonists: can bind to a receptor but result in only partial functional response, independent of the amount of drug administered, eg, buprenorphine
- Most clinically administered opioid analgesics bind to µ (MOP)

Opioids have benefits for many patients with chronic pain

- Not all patients become dependent or addicted
- Most patients do not experience overdose and death
- Many patients respond well if not at first to one opioid, then to an alternative opioid(s) and at doses within recommended ranges
- But not all types of chronic pain are optimally treated with opioid therapy:
  - Headache
  - Fibromyalgia
  - Chronic abdominal pain
- However, there may be more than one pain type in a given patient

Proposed critical thinking model for chronic opioid therapy

Need to balance access to pain medications with misuse and abuse prevention
**Goals of clinical assessment**

- Achieve diagnosis of pain
- Identify and treat underlying causes of pain
- Identify and treat comorbid conditions
- Evaluate psychosocial factors
- Evaluate functional status (activity levels)
- Set goals
- Develop a targeted treatment plan
- Determine whether a consultation is needed

**Evaluation of the patient**

- Medical history
- Physical exam including pain assessment
- Review of prior work up, diagnostic tests, prior treatment
- Document the nature, intensity, location of pain, effect of pain on physical and psychological function
- History of substance abuse

**Risk stratification**

- Age ≤ 45 years
- Gender
- Family history of prescription drug or alcohol abuse
- Cigarette smoking

**Risk factors for aberrant behaviors/harm**

- Biological
  - Substance use disorder
  - Preadolescent sexual abuse (in women)
  - Major psychiatric disorder (e.g. personality disorder, anxiety or depressive disorder, bipolar disorder)
- Psychiatric
  - Prior legal problems
  - History of motor vehicle accidents
  - Poor family support
- Social
  - Involvement in a problematic subculture

**10 Principles of universal precautions**

1. Diagnosis with appropriate differential
2. Psychological assessment including risk of addictive disorders
3. Informed consent (verbal or written/signed)
4. Treatment agreement (verbal or written/signed)
5. Pre-/post-intervention assessment of pain level and function
6. Appropriate trial of opioid therapy/adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the “Four A’s” of pain medicine: Analgesia, Activity, Adverse Reactions, and Aberrant Behavior
9. Periodically review pain and comorbidity diagnoses, including addictive disorders
10. Documentation

**Opioid risk assessment and guidance**

- Questionnaires
  - Current Opioid Misuse Measure (COMM)
  - Diagnosis, Intractability, Risk, and Efficacy (DIRE)
  - Opioid Risk Tool (ORT)
  - Screener and Opioid Assessment for Patients in Pain (SOAP-P)
  - Screening Instrument for Substance Abuse Potential (SISAP)
- Opioid treatment agreement
- Reviewing PDMP information
- Urine drug testing (UDT)
- Abuse deterrent opioid formulations
- Ongoing patient monitoring
Opioid Risk Tool

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<th>Male</th>
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<tr>
<td>Prescription drugs</td>
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<td>3. Age (mark box if between 16 and 45 years)</td>
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<tr>
<td>4. History of preadolescent sexual abuse</td>
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<tr>
<td>5. Psychological history</td>
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<tr>
<td>Depression</td>
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Scoring totals

Administration
Initial visit
Prior to opioid therapy
Scoring
0-3 (0%): low risk
0-0.3 (3%): moderate risk
0-1 (15%): high risk

ADD, attention deficit disorder; ODD, obsessive-compulsive disorder.

Principles for responsible prescribing

- I have resolved key points before initiating opioid therapy
  - Diagnosis established and opioid treatment plan developed
  - Established level of risk
  - I can treat this patient alone? Need to enlist other consultants to co-manage this patient (pain or addiction specialists)
- I have considered nonopioid modalities
  - Pain rehabilitation program
  - Behavioral strategies
  - Non-invasive and interventional techniques

Medical history influences risk of overdose

- The diagnosis of any of the following medical conditions increases the risk of overdose
  - Sleep apnea
  - Chronic obstructive pulmonary disease
  - Asthma
  - Chronic kidney disease
  - Liver function abnormalities
  - HIV infection
- Risk is also influenced by
  - Post traumatic stress syndrome
  - Other psychological or psychiatric conditions

Patient background and personal history influences risk of death from overdose with prescription opioid analgesics

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
</tr>
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| Demographics                      | • Gender (male?)
|                                   | • Between the ages of 45-54 years
|                                   | • White or Native American                       |
| Socioeconomic                     | • Residing in a rural area
|                                   | • Low income
|                                   | • Community Medical                              |
| Substance abuse                   | • Alcohol consumption
|                                   | • Long-term opioid use
|                                   | • Recent medical care for opioid poisoning or intoxication
|                                   | • Recent released prisoner or from a mandatory abstinance or drug court program
|                                   | • History of substance abuse                     |
| Prescription drug use             | • Filling of multiple prescriptions [doster shopping]?
|                                   | • Concurrent use of ONS depressants such as benzodiazepines and tricyclic antidepressants
| Other                             | • Military veteran
|                                   | • Mental health problem                           |

Risk of opioid use disorder based on patient behaviors

Lower Risk
- Stable pattern of medication use
- Improvement in overall function while on medication
- Expresses concerns about side effects
- Has left medication
- Does not seek additional opioids once adequate analgesia is achieved

Higher Risk
- Loss of control with medication
- Decrease in overall function while on medication
- Ignores persistent adverse effects
- Does not follow treatment plan
- Does not have leftover medication
- Continues to seek opioids despite adequate analgesia

Risk of overdose for bystanders: children and teenagers

- Young children and teenagers are exposed to prescription opioids that are prescribed for others, most commonly at home1.
- A RADARS study (2003–2006) found that nearly all exposures to prescription opioids in children <6 years old involved ingestion (99%) and occurred in the home (92%)2.
  - In 9,179 children, exposures were associated with 8 deaths.
- A 10 year study of pediatric poisonings compared against adult prescriptions found adult medications significantly associated with exposures and poisonings in children of all ages with the strongest association for opioids3.
  - Across medications, the greatest risk was among children <5 years old, then 3–19 year-olds.
  - Rates of FD visits were highest for hypoglycemics (60.1%) but serious injuries and hospitalisations occurred most frequently with opioids (26.8%, 35.2%, respectively).
- Every day, 2,500 US adolescents, aged 12–17, abuse a prescription pain reliever for the first time4.

Demographics of unintentional opioid analgesic-related deaths

The incidence of opioid analgesic-related deaths has increased 125% in the 15-24 year-old age group. The greatest incidence of opioid-related deaths is in the 45–55 year-old age group.

Most opioid analgesic prescriptions in the US are for short-acting opioid analgesics (SAOAs)

- More than 50% of opioid analgesic users are taking SAOAs:
  - Long acting opioid analgesics (LAOAs) have a longer duration of analgesic action, but a potentially longer onset of action, or both6.
  - SAOAs available in combination with acetaminophen or an NSAID have a limited maximum daily dose.
  - Due to risk of liver and gastrointestinal toxicity mediated by non-opioid component.
  - This may prevent titration of opioid to adequate dose.
  - SAOAs and LAOAs can be effective for chronic pain.
  - Direct comparisons in efficacy and safety are scarce.
  - The increase in SAOAs use is in part driven by changes in how they are used: in the 5 years prior to 20137:
    - The number of prescriptions per patient increased.
    - The number of days SAOAs were prescribed increased.

Most patients prefer SAOAs

- Preference for SAOAs is vis a vis analgesia.
- They use less opioid – but more often – when SAOAs alone is used compared with both a LAOA plus SAOA.
- The trend for longer-term use of short-acting prescription opioids is concerning, as extended use of these agents can lead to an increase in drug tolerance and subsequent dependence.

Dependence (physical) is not addiction

- Addiction* can include dependence but is distinguished by compulsive drug seeking and use, despite sometimes devastating consequences.

SAOAs:
- Vicodin® (hydrocodone with acetaminophen) 48.1
- Lortab® (oxycodone and acetaminophen) 16.7
- Percocet® (oxycodone with acetaminophen) 13.6
- Vicodin® (hydrocodone with acetaminophen) 8.3
- Tylox® (codeine with acetaminophen) 3.9

LAOAs:
- OxyContin® (oxycodone) 8.3
- Vicodin® (hydrocodone with acetaminophen) 3.8
- Actiq® (fentanyl citrate) 1.6

2Managed care pharmacy data used to demonstrate the increasing trend in non-medical use of opioids, 2001–2008: Data adapted from (1).
3 3http://www.mtregis.com/opiates/effects
4http://www.mtregis.com/opiates/effects
5http://www.mtregis.com/opiates/effects
6http://www.mtregis.com/opiates/effects
7http://www.mtregis.com/opiates/effects
8http://www.mtregis.com/opiates/effects
Considerations for opioid analgesics in pain management: implications for risk of overdose

- Variability in dose requirements
- Variation in susceptibility to side effects
- Varying potency among opioids (opioid equivalence)
  - Can result in differences in side effect profiles
  - These differences can be genetic in origin
- Presence of co-morbidities
- Depression, may be underdiagnosed
- Insomnia, very common in patients with chronic pain
- Dose regimens and tolerance
- Variability in outcomes (starting pain intensity and degree of relief with opioid) measurements

Clinical interface between pain and addiction

- Pain and addiction are complex; both have strong behavioral components
- Both the addition and pain systems are dependent on opioid agonist activity at the mu-receptor
- Both the treatment of pain with opioid analgesics and abuse of opioids interact at the brain-reward center in the limbic system, which leads to feelings of pleasure or reward
- Genetic data suggest that pain, opioid analgesia, and opioid addiction may share similar patterns of gene expression
- The goals of pain treatment are to reduce pain and suffering, enhance quality of life, and increase the ability to function, which requires achieving a balance between treating the pain and avoiding diversion and abuse
- Developing and following a treatment plan, and monitoring behaviors of patients treated with opioid analgesics can help achieve treatment goals

Opioid overmedication and potential for overdose

OVERMEDICATION
- Unusual sleepiness or drowsiness
- Mental confusion
- Slurred speech
- Slow or shallow breathing

POINTER
- Pinpoint pupils (miosis)
- Slowed heartbeat
- Low blood pressure
- Difficulty waking the person

OVERDOSE
- Face clammy and pale
- Body is limp
- Fingernails and lips tinged blue or purple
- Vomiting/gurgling noises
- Respiration and/or heart beat very slow or stopped
- Cannot be awakened
- Death rattle

Naloxone in clinical practice

Naloxone has been approved in the US for reversal of the effects of opioid overdose since 1971

Injection indicated for complete or partial reversal of opioid depression
- Dosing initiated at 0.4-2 mg and repeated at 2-3 min intervals until patient responds with adequate spontaneous breathing
- Rapidly distributed throughout the body
- $C_{max}$: 1.07 ng/mL
- $T_{max}$: 20 min
- Duration of effect 30-60 min; further doses may be required if patient has taken long-acting opioids

Criteria for substance use disorder diagnosis

A patient must meet at least 2 criteria

- Criteria 1: 2–3 criteria, mild
- Criteria 2: 4–5 criteria, moderate
- Criteria 3: 6–7 criteria, severe

Strategies for prevention of overdose

- Education of drug users
- Family support groups
- Motivational post-overdose interviews
- Supervised injecting rooms
- Provide naloxone for home use
- Encourage prescribers to use state Prescription Drug Monitoring Program (PDMPs)
- Assessment of patient: Obtain history of the patient’s past drug use
- In emergency situations, the physician should prescribe the smallest possible quantity (typically not exceeding 3 days’ supply) and arrange for return visit the next day

Criteria for substance use disorder diagnosis

- Continuing to use opioids despite negative personal consequences
- Repeatedly unable to carry out major obligations at work, school, or home due to opioid use
- Recurrent use of opioids in physically hazardous situations
- Continued use despite persistent or recurrent physical or psychological difficulties from using opioids
- Continued use of the same amount of a substance is used to avoid withdrawal
- Using greater amounts or using over longer time periods than intended
- Persistent desire or unsuccessful efforts to cut down or control opioid use
- Spending a lot of time obtaining, using, or recovering from using opioids
- Stopping or reducing important social, occupational, or recreational activities due to opioid use
- Insufficient use of opioids despite acknowledgment of persistent or recurrent physical or psychological difficulties from using opioids
- Craving or a strong desire to use opioids
Mitigation of overdose risk in people with pain

- Risk exists for both people with pain, and people with substance use disorders
  - And, of course, in those with both
- There is a recent trend toward increased prescribing of naloxone for use in case of unintentional overdose
- Much of the focus in this area has been for people without a legitimate medical need for opioids as part of a pain care plan
- When should naloxone prescribing be considered for people with pain who use opioids for pain relief?

Recommendations for safe and effective use of opioid analgesics for chronic noncancer pain

1. Opioid analgesic treatment agreement
2. Screen for prior or current substance abuse/misuse (alcohol, illicit drugs, heavy tobacco use)
3. Screen for depression
4. Prudent use of random urine drug screening (abuse, non-prescribed drugs)
5. Do not use concomitant sedative-hypnotics or benzodiazepines
6. Track pain and function to recognize tolerance and track effectiveness
7. Track daily MED using an online dosing calculator
8. Seek help if MED exceeds 80–120 mg and pain and function have not substantially improved
9. Use the state Prescription Drug Monitoring Program to monitor all sources of controlled substances

What is the “Good Samaritan Policy”?

- Provides immunity for people administering naloxone or obtaining treatment for someone experiencing an overdose
- Provides responsible action by people reluctant to act due to legal concerns
- Several states have now amended laws to encourage “Good Samaritan” to seek medical assistance

Putting naloxone into the hands of bystanders (overdose witnesses)

THIRD-PARTY PRESCRIBING

Several states have introduced legislation allowing physicians to prescribe naloxone to a third party who can give naloxone when indicated

STANDING ORDER

In some cases, physicians can issue a standing order allowing non-medical personnel to distribute naloxone to those they consider at risk for possible overdose

Potential concerns regarding approved formulations when in position to use naloxone for overdose victim

HCP
- Paramedics
- Hospital DO staff
- Police DO staff

Risk of needle-stick injury and contracting blood-borne viral infections when injecting individuals who are drug users
- Limited for access in individuals with drug use

Non-HCP
- Law enforcement
- Social service workers
- Harm reduction outreach

Risk of needle-stick injury and contracting blood-borne viral infections when injecting individuals who are drug users
- Limited for access in individuals with drug use

All Prescribers Play an Active Role in Reducing the Risks Associated With Opioids

- When opioids are being considered as part of a chronic pain treatment plan:
  - Establish diagnosis
  - History and physical
  - Relevant diagnostic tests
  - Complete an appropriate risk assessment PRIOR to prescribing
  - Monitor the patient regularly on an ongoing basis
  - Recognize that all patients are at risk
  - Prescribe opioids as part of a multimodal treatment regimen

Conclusions

- Opioid analgesics remain among the most commonly prescribed medications for people experiencing chronic pain.
- Among the many adverse effects of chronic opioid therapy is the potential for misuse, abuse and unintentional overdose resulting in significant morbidity including death.
- Multiple practical steps can be instituted by the prescriber to help reduce the risk of misuse and abuse as well as reduce the risk of unintentional overdose.