Colorado's Opioid Solution: Clinicians United to Resolve the Epidemic (CO's CURE)

The Rocky Mountain Chapter of the Society of Hospital Medicine

2020 Opioid Prescribing and Treatment Guidelines for the Medical Inpatient

Developed by the Rocky Mountain Chapter of the Society of Hospital Medicine in partnership with Colorado Hospital Association, Colorado Medical Society and Colorado Consortium for Prescription Drug Abuse Prevention

COLORADO MEDICAL SOCIETY

COLORADO CONSORTIUM for Prescription Drug Abuse Prevention

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Dedicated to the clinicians across Colorado and the patients for whom they care.

Contributors

Editor-in-Chief

Donald E. Stader III, MD, FACEP

Hospitalist Editors

Caitlin Dietsche, MD
Darlene Tad-y, MD, SFHM
Cathy O'Neil, MD
Eric Howell, MD, MHM

Associate Editors

Elizabeth Esty, MD

Section Editors

Robert Valuck, PhD, RPh, FNAP
Introduction
Rachael Duncan, PharmD, BCPS, BCCCP
Limiting Opioid Use in the Hospital
Jonathan Clapp, MD
Alternatives to Opioids for the Treatment of Pain
Martin Krsak, MD
Donald E. Stader III, MD, FACEP
Harm Reduction
Elizabeth Esty, MD
Steven Young, MD
Treatment of Opioid Use Disorder
Debra Parsons, MD, FACP,
Donald E. Stader III, MD, FACEP
Darlene Tad-y, MD, SFHM
Robert Valuck, PhD, RPh, FNAP
The Future and Ending the Opioid Epidemic in Colorado

Contributing Editors

Kevin Boehnke, PhD
Julie Denning
Kenneth Finn, MD
Lisa Kisling Thompson, DO
Helena Winston, MD
Narin Wongngamnit, MD

Task Force Members and Volunteers

Jessica Devitt, MD
Mark Gaynor, MD
Christine Johnston, MD
Jennie Johnson, PA
Clark Lyda, PharmD
Abigail Mehler, PA-C
Nathan Novotny
Nathan Odom, MD
Sarah Scarpato, MD
John Spartz
Anunta Virapongse, MD, MPH/MSPH

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Introduction

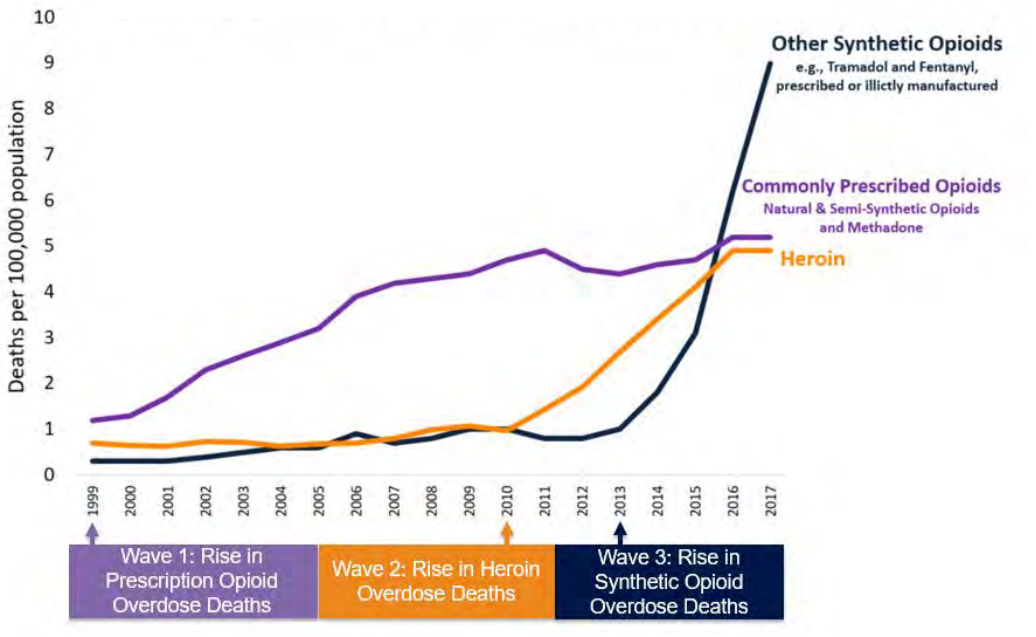
Clinicians across Colorado and the nation are facing one of the most devastating public health crises of a generation. Opioids, both prescription and illicit, have become the leading cause of accidental death in the United States for adults 50 years of age or younger.[1] Opioid-related adverse drug events (ORADEs), accidental overdose, physical dependence and the development of opioid use disorder (OUD) have become an increasingly common part of medical practice. The number of lives impacted by the crisis is astonishing. The Centers for Disease Control and Prevention (CDC) reports that opioid overdose killed nearly 400,000 Americans between 2000 and 2017,[2] and currently an average of 130 people die every day in the United States of opioid overdose **(FIGURE 1)**.[3]

More than 10.3 million people in the United States over the age of 12 years self-reported misusing opioids in 2018, with 9.9 million misusing prescription pain relievers and 808,000 using heroin.[4] The pharmaceutical use of opioids first skyrocketed between 1990 and 1996; prescriptions for fentanyl rose 1,000%, followed by morphine (49%), oxycodone (15%) and hydromorphone (12%).[5] The number of prescription opioids sold in the United States increased five-fold between 1999 and 2017, and prescription opioids were involved in 218,000 overdose deaths during this same time.[5] In 2017, there were 58 opioid prescriptions written for every 100 people in the United States, with the average prescription length of 18 days.[6]

The dire consequences of the widespread availability of prescription opioids in the United States emerged over time. The "lag period" between first exposure to an opioid (either medical or nonmedical) and first treatment admission is, on average, about seven years; between first exposure and overdose death is between nine and 13 years.[7,8] In 2017, opioids accounted for 34% of all admissions for substance use disorder (SUD) treatment in people aged 12 years and older.[9] The economic implications of this epidemic are staggering. The nonmedical use of opioid pain relievers has cost society approximately $1 trillion between 2001 and 2016 and, unless major changes are made, the financial impact is projected to grow by another $500 billion by 2020.[10]

(FIGURE 1)

Three Waves of the Rise in Opioid Overdose Deaths, 1999-2017

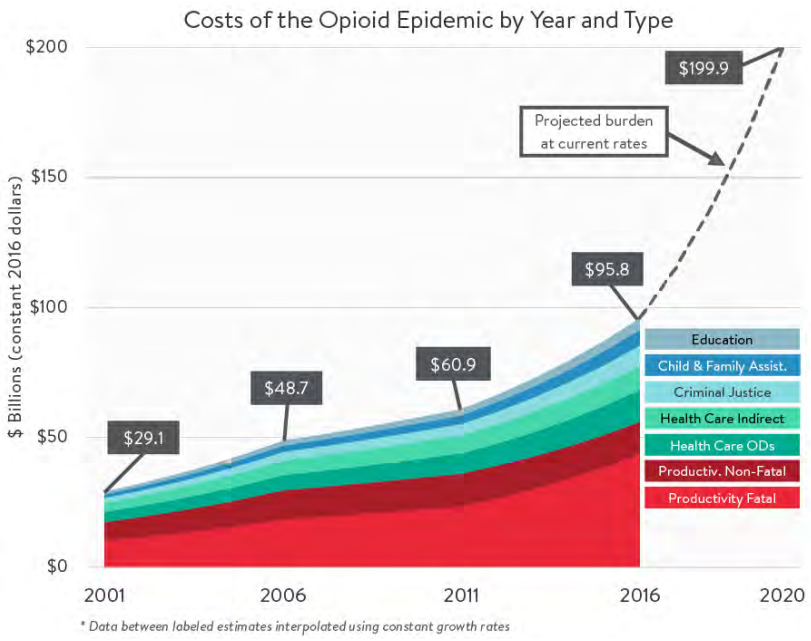


SOURCE: National Vital Statistics System Mortality File

Introduction continued

(FIGURE 2)

Total and Projected Costs of the Opioid Epidemic, 2001-2016



SOURCE: Altarum[10]

While a number of external factors have contributed to the use of these potentially lethal drugs, the medical community is compelled to acknowledge its role in this crisis. Fortunately, clinicians and health care systems also have the power to reverse these grim statistics by reforming their practices with resolve and innovation. Although CO's CURE acknowledges the value of opioids in certain clinical situations, such as for end-of-life care and the treatment of pain associated with sickle cell disease, severe trauma, burns and cancer, it advocates using extreme caution in all cases.

These guidelines are meant to inform and augment clinical judgment, not replace it. What follows is a compilation of ideas and suggestions that can be implemented by hospitals and clinicians to aid in the prevention of opioid misuse and addiction and the identification, treatment and support of patients with OUD. It is unlikely that a hospital can or should attempt to implement each strategy or idea included in these guidelines. Rather, hospitals should consider which of these suggestions are most appropriate given their unique processes and resources. The suggestions in these guidelines should not be viewed as a substitute for the oversight of legal counsel and compliance leaders.

The Opioid Epidemic in Colorado

Coloradans have been significantly affected by this nationwide public health crisis. Since 2000, Colorado has seen 6,030 overdose deaths from opioids.[11] There were 1,635 prescription opioid-related overdose deaths in Colorado from 2013 to 2017, translating to a rate of 5.8 deaths per 100,000 Colorado residents.[12] Heroin-related opioid overdose deaths increased 76% from 2013 to 2017.[12]

Colorado Statistics

In 2017, in the state of Colorado:

- There were over 3.7 million opioid prescriptions dispensed to one million patients at retail locations **(TABLE 1)**. These numbers fell slightly from a high of 4.3 million opioid prescriptions for 1.1 million patients in 2015.[12]
- There were 1,012 drug overdose deaths, 57% of which involved an opioid.[12]
- 15% of opioid-naive patients were prescribed long-acting opioids.[13]
- 10% of patient prescription days had overlapping opioid and benzodiazepine prescription use.[13]
- There were 671.3 opioid prescriptions filled per 1,000 residents.[13]
- There were 134.3 treatment admissions for heroin per 100,000 people and 40.6 treatment admissions for pharmaceutical opioids per 100,000 people.[1]

Introduction continued

(TABLE 1)

Characteristics of Opioid Prescriptions Dispensed, Colorado 2014-2017

Characteristics	2014	2015	2016	2017
Number of Prescriptions Dispensed	4,039,048	4,310,254	4,159,575	3,765,253
Number of Unique Patients	1,085,551	1,131,781	1,102,297	1,027,685
Number of Unique Prescribers	25,011	24,784	28,063	27,676
Number of Unique Pharmacies	941	839	1,039	1,097

Excludes buprenorphine drugs commonly used to treat opioid use disorder
In 2014 NPI was used to identify unique prescribers and pharmacies as DEA numbers were not available until 2015

SOURCE: Colorado Opioid Profile[12]

(TABLE 2)

High-Risk Prescribing Practices and Patient Behaviors, Colorado 2014-2017

Indicators	2014	2015	2016	2017	2014-2017 % Change
Patients receiving more than 90 MME (%)	10.3	8.9	8.7	8.2	-20.5
Patients with MPEs (rate/100,000 residents)	170.1	124.0	93.6	68.0	-60.0
Patients prescribed LA/ER opioids who were opioid-naive (%)	18.2	17.6	15.8	15.1	-17.3
Patient prescription days with overlapping opioid prescriptions (%)	22.3	21.5	21.4	20.5	-7.8
Patient prescriptions days with overlapping opioid and benzodiazepine prescriptions (%)	12.1	11.6	11.2	9.9	-18.0

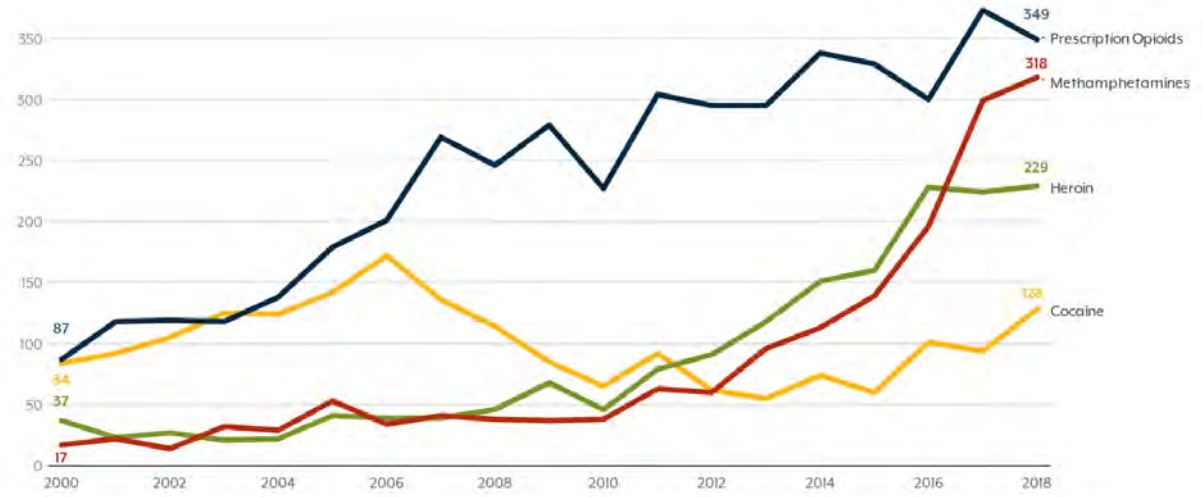
Schedule II-IV Controlled Substances
Excludes Buprenorphine drugs commonly used for treatment
Annual percentages are based on average of quarterly percentages
Data Source: Vital Statistics Program, CDPHE and the Colorado Prescription Drug Monitoring Program, DORA
Data Analysis by: CDPHE, 2018

SOURCE: Colorado Opioid Profile[12]

Introduction continued

(FIGURE 3)

Number of Drug Poisoning Deaths in Colorado by Drug Type, 2000 - 2018



Categories are not mutually exclusive (may total to more than 100% of total drug overdoses) or comprehensive (other drugs not listed).

SOURCE: Colorado Health Institute[14]

While there is considerable variation from county to county in Colorado, with some rural counties particularly hard-hit, the impact of the opioid crisis is felt in all regions and communities. No county is untouched, and the need to address the effects of the crisis is universal. All Colorado physicians, health care practitioners and hospitals must work together to turn the tide and resolve the crisis.

The Origins of the Opioid Epidemic

Concerned about potential adverse effects, including addiction and overdose, few physicians prescribed opioids for chronic noncancer pain throughout most of the 20th century.[15] That changed in 1986, however, when pain expert Russell Portenoy published a limited case series of 38 hospital patients that suggested that chronic noncancer pain could be managed safely with high doses of opioids without posing a risk of addiction.[16] Since then, the scientific validity of Portenoy's original work has been called into question; in recent years, the researcher himself has publicly doubted the relative efficacy and safety of long-term opioid use for the treatment of chronic noncancer pain.[17-20] Portenoy's findings were endorsed by both the American Academy of Pain Medicine and the American Pain Society, which further legitimized his assertions about the safety of opioid medications.[21]

As a result, many pharmaceutical companies began to aggressively market opioids for wider use at increased dosages and in extended-release formulations.

This shift in perspective was reinforced by the Veterans Health Administration, which adopted pain as the "fifth vital sign" in 1999.[22] The Joint Commission, a governing body responsible for hospital accreditation, added pain management as a requirement for accreditation in 2000.[2,15] During the same period, a report by the Institute of Medicine, *Relieving Pain in America,* painted pain management as a "moral imperative, a professional responsibility, and the duty of people in the healing professions."[23] In addition to these mounting institutional pressures, patient satisfaction surveys increasingly compelled medical providers to place a premium on pain management. These highly subjective scorecards, which were routinely linked to remuneration, used the management of pain as a marker for patients' satisfaction with the care they received.[24,25] The rising popularity of patient satisfaction surveys and similar ideologies further fueled this campaign, resulting in a 400% rise in U.S. opioid sales from 1999 to 2014.[26] Once reserved for the treatment of severe pain, opioid analgesics became routinely prescribed for a wide range of pain complaints.

Introduction continued

Many hospitalists feel conflicted about the use of opioids during admissions. In a study that interviewed 25 hospitalists to understand their attitudes, beliefs and practices towards opioid prescribing during hospitalization and at discharge, the majority of participants felt prescribing opioids to inpatients can successfully treat acute pain; however, they also demonstrated concern about contributing to the development of future OUD in their patients.[27] Prior to the 2018 position statement by the Society of Hospital Medicine (SHM), "Improving the Safety of Opioid Use for Acute Noncancer Pain in Hospitalized Adults: A Consensus Statement From the Society of Hospital Medicine," formal guidance in the use of opioids in hospitalized medical patients had been lacking. The Rocky Mountain Chapter of the SHM and CO's CURE leadership aim to offer further guidance through these *2020 Opioid Prescribing and Treatment Guidelines for the Medical Inpatient.* The intent of these guidelines is to provide hospitalist clinicians with evidence-based information regarding best practices in the treatment of adult medical inpatients presenting with pain, opioid stewardship in hospitalist practice, use of alternatives to opioids for pain management, strategies for harm reduction and identification and treatment of patients with OUD.

CO's CURE

Faced with this enormous public health crisis, Colorado clinicians are taking a stand for the benefit of all. CO's CURE is developing the nation's first set of comprehensive, multispecialty medical guidelines designed to end the opioid epidemic. Within each specialty, there is room for specific nuances of practices, and across all CO's CURE guidelines, there is multispecialty collaboration with input from content experts. Four pillars anchor the clinical guidelines and provide an evidence-based pain and addiction management approach:

1. Limiting opioid usage
2. Using alternatives to opioids (ALTOs) for the treatment of pain
3. Implementing harm reduction strategies
4. Improving treatment and referral of patients with OUD

These pillars were conceived by the Colorado Chapter of the American College of Emergency Physicians and implemented in Colorado emergency departments in 2017 through the Colorado Opioid Safety Pilot and later the Colorado ALTO Project, which were led by Colorado Hospital Association. The Colorado Opioid Safety Pilot resulted in a 36% decrease in opioid use as well as a 31% increase in the use of ALTOs for pain management in 10 pilot EDs over the six-month study period.[28] The success experienced in Colorado emergency departments through those initiatives represent just one front of efforts to confront the opioid epidemic in Colorado. To fully resolve the opioid epidemic, Colorado health care providers will need to adopt a more inclusive, coordinated and ambitious approach.

Now is the time for all specialties and clinicians to unite, to create better treatment paradigms for the benefit of the health care system, patients and Colorado's communities. The guidelines developed under CO's CURE represent some of the most forward-thinking and comprehensive strategies in the nation. They belong to not one specialty, but to all specialties; rather than divide clinicians into their respective tribes and silos, they unite them in a common cause – to address and resolve the opioid epidemic in Colorado and beyond.

Limiting Opioid Use in the Hospital

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Limiting Opioid Use in the Hospital

The majority of patients who develop OUD report that their first exposure to an opioid involved a pain medication that was prescribed to them or diverted from a family member or friend.[26] Hospitalists comprise a relatively small component of U.S. outpatient opioid prescribing. From 2016 to 2017, hospitalists accounted for 0.2% of all dispensed opioid prescriptions with nearly 400,000 prescriptions.[29] While hospitalists are not high-frequency opioid prescribers, hospitals and inpatient admissions represent an important area of exposure for opioid-naive patients. One multicenter retrospective study of 1.14 million non-surgical admissions found that 51% of patients received an opioid medication during hospitalization and 23% of those patients received ≥100 mg of oral morphine equivalents per day.[30] The same study identified significant heterogeneity of practice, with opioid prescribing rates ranging from 33% to 64%.[30]

Opioids serve as a mainstay of pain management in the hospital setting and can place patients at risk not only of developing OUD, but also of significant immediate side effects. Opioid-related adverse drug events (ORADEs) are associated with higher hospital costs, prolonged length of stay and substantial health care resource usage.[31] Hospitals with higher rates of inpatient opioid prescribing had higher rates of ORADEs, and 0.6% of hospitalized medical patients experienced a serious ORADE.[30] The potential for immediate and long-term harm to patients and the risk of diversion and misuse of opioids prescribed on discharge call for better opioid stewardship by hospitalist clinicians. Across all specialties, a first step to address the epidemic of OUD is to decrease the frequency and ease with which opioids are ordered and prescribed to opioid-naive or relatively opioid-naive patients. Hospitalist clinicians play a vital role in screening patients, ordering and prescribing opioids conservatively and providing thorough counsel on safe use of opioids prior to discharge.

NOTE: The following practice recommendations may not apply to patients who are dependent on opioids, such as those with active OUD, those on medication-assisted treatment (MAT) and those receiving chronic opioid therapy (COT) for pain. Special considerations for the care of these patients are addressed below in "Harm Reduction" and "Treatment of Opioid Use Disorder" sections.

Practice Recommendations

Deciding When to Use Opioids During Hospitalization

1. **Opioids can be dangerous drugs with significant potential for misuse and addiction, numerous side effects, lethality in overdose, rapid development of tolerance and debilitating withdrawal symptoms. Clinicians are encouraged to reserve opioids for the treatment of severe pain, pain that has not responded to nonopioid therapy and cases where nonopioid therapy is contraindicated or anticipated to be ineffective.**
   a. Opioids are among the three broad categories of medications with potential for misuse, dependence and addiction, the other two being central nervous system (CNS) depressants and stimulants. Opioids act by attaching to opioid receptors on nerve cells in the brain, spinal cord, gastrointestinal (GI) tract and other organs, triggering a spike in dopamine that not only reduces the perception of pain, but can also manufacture a powerful sense of well-being and pleasure by affecting the brain's limbic reward system.
   b. When used repeatedly, opioids induce tolerance as higher doses are required over time to produce the same effects.[32] This mechanism also contributes to the high risk of overdose following a period of abstinence.[33] Tolerance can be lost in times of abstinence, leading relapsed users to take a previously "safe" dose with disastrous results.[34] The effects of opioids are mediated by specific subtype opioid receptors (mu, delta and kappa) that are also activated by endogenous endorphins and enkephalins. The production of endogenous opioids is inhibited by the repeated administration of outside opioids, which accounts for the discomfort that ensues when the drugs are discontinued.
   c. Opioid therapy is associated with a number of common, sometimes serious side effects, including sedation, respiratory depression, constipation, nausea and vomiting **(TABLE 3)**.[26,55] These complications, which often necessitate additional medical care, can prevent patients from performing daily tasks and remaining active in the workforce.[35]

Limiting Opioid Use in the Hospital continued

(TABLE 3)

Side Effects of Opioids

Common Side Effects	Serious Side Effect of Chronic Opioid Use
• Nausea/vomiting • Constipation • Pruritus • Euphoria • Respiratory depression, particularly with the simultaneous use of alcohol benzodiazepines, antihistamines, muscle relaxants or barbiturates • Lightheadedness • Dry mouth	• Cardiac abnormalities, including prolonged QTc and torsades de pointes[56] • Sudden cardiac death with the concomitant use of benzodiazepines and methadone[57] • Hormonal disruptions, including decreased testosterone in males[58] • Decreased luteinizing hormone, follicle-stimulating hormone, and fertility in women[59] • Musculoskeletal compromise, including an increased risk of osteoporosis[60] • Immunosuppression[61] • Inhibition of cellular immunity via delta and kappa receptors[62] • Hyperalgesia (i.e., upregulation of receptors and increased tolerance)[63] • Sleep disturbances (e.g., shortened deep sleep cycle)[64] • Delayed or inhibited gastric emptying, increased sphincter tone, and blockade of peristalsis[65]

d. The risk-to-benefit ratio of opioid therapy does not support the use of opioids in low-severity pain management. Nonopioid analgesics, including acetaminophen (APAP) and non-steroidal anti-inflammatory drugs (NSAIDs), have been shown to be equally or more effective in managing many types of pain when compared to opioid medications.[36-40]

2. Prior to administering an opioid, physicians are encouraged to perform a rapid risk assessment to evaluate a patient's potential for developing OUD and to identify medical comorbidities that increase the risk of ORADEs. Alternative methods of pain control may be sought for patients at increased risk for OUD or ORADEs, and it is recommended that hospitalists exercise particular caution when administering opioids to patients at elevated risk for OUD or ORADEs.

a. Multiple agencies, including the CDC and the Colorado Department of Regulatory Agencies, advocate using an opioid risk tool to evaluate for factors that might predispose patients to addiction and misuse. While this approach has only been validated in cases of chronic pain, screening tools may help hospitalists identify high-risk patients.[41]

b. High-risk criteria include:
   i. Personal or family history of SUD (e.g., alcohol, illicit/prescription drugs)
   ii. Age between 16 and 45 years
   iii. Behavioral health diagnosis (e.g., depression, attention deficit disorder, bipolar disorder, schizophrenia)
   iv. History of sexual abuse or childhood trauma

c. Hospitalists should be aware that no validated screening tools exist for the identification of patients at no or low risk for developing OUD. It is important to consider the potential vulnerability of every patient.

d. Hospitalists are encouraged to consider comorbid health conditions and exercise caution when ordering or prescribing opioids to patients at increased risk for adverse drug reactions and/or accidental overdose.

e. High-risk comorbidities and risk factors include:
   i. Pulmonary comorbidities (e.g., chronic obstructive pulmonary disease, sleep apnea)
   ii. Cardiac comorbidities (e.g., congestive heart failure)
   iii. Organ dysfunction (e.g., renal or hepatic failure)
   iv. Elderly age
   v. Combining opioids with other sedatives[42]
   vi. Prior SUD diagnosis[42]

Limiting Opioid Use in the Hospital continued

f. Opioids may still be cautiously utilized for the management of pain in patients determined to be at increased risk for OUD or ORADEs. If the decision to use opioids for pain management is made in patients with risk factors for either or both OUD and ORADEs, consider a reduced starting opioid dose and closer monitoring for adverse effects.

3. Hospitalists are encouraged to review the information contained in the Colorado Prescription Drug Monitoring Program (PDMP) to inform decision making around opioid therapy during hospitalization and upon discharge.

a. 2014 Colorado House Bill (HB) 14-1283 requires all Colorado-licensed prescribing practitioners with Drug Enforcement Administration (DEA) registrations to create an account with the Colorado PDMP.[43]
b. Drug monitoring programs have been shown to influence opioid prescribing practices, especially in the case of lost or long-term prescriptions.[44]
c. These programs can aid providers in identifying patients with multiple recent prescriptions from multiple providers and help identify those already using other controlled medications on a chronic basis.[45]
d. Although there is limited data to indicate the impact of PDMPs on patient outcomes, these programs can prompt referral to support services, initiation of MAT and/or consultation with a pain management or addiction specialist.
e. Along with information gathered from PDMPs, concerns about possible misuse of controlled substances or the presence of SUD can prompt further conversations between physician and patient.
f. Information from PDMPs does not preclude the use of opioids for treatment of acute pain during hospitalization but can be incorporated into the analysis of the risks and benefits of opioid therapy.

4. Hospitalists are encouraged to educate patients and families or caregivers about the potential risks and side effects of opioid therapy, as well as the availability of alternative pharmacologic and nonpharmacologic therapies for managing pain.

a. Patients are often not aware of the risks associated with opioid medications or that there may be equally effective alternatives to opioids available for the treatment of pain.
b. Ideally, a discussion of the risks of opioid medications as well as the availability of alternative pharmacologic and nonpharmacologic therapies should be conducted prior to initiating treatment with an opioid.
c. Hospitalists are encouraged to inform patients that they may request nonopioid therapy even to treat severe pain.

5. Hospitalists are encouraged to work with patients and families or caregivers to establish realistic goals and expectations of opioid therapy and the expected course of recovery.

a. Discussing expectations with patients and their families or caregivers at the start of therapy is necessary to facilitate a clear understanding of how meaningful improvement will be defined and measured during hospitalization as well as how long the patient is anticipated to require opioid therapy.
b. Hospitalists are encouraged to discuss with patients, families or caregivers that the goal of opioid therapy is tolerability, not elimination, of pain such that meaningful improvement in function can be achieved.
c. It may also be communicated that a decrease in pain intensity in the absence of improved function is not considered meaningful improvement in most situations and, ideally, will prompt reevaluation of the appropriateness of opioid therapy as well as close follow up with a clinician after hospital discharge.
d. Discussions regarding the expected course of recovery can also include that acute pain is expected to resolve as the underlying medical condition improves. Hospitalists are encouraged to educate patients and families or caregivers that although pain may persist beyond the hospitalization, pain that is severe enough to require opioids will often be resolved or nearly resolved by the time of hospital discharge.

Limiting Opioid Use in the Hospital continued

Minimizing Harm with Opioid Therapy During Hospitalization

6. **When opioids are deemed a necessary part of the analgesic plan, hospitalists are encouraged to use the lowest effective opioid dose for the shortest possible duration to manage pain.**
   a. Higher doses of opioids are associated with higher incidence of ORADEs, particularly overdose, in both inpatient and outpatient settings.[46,47]
   b. Ideally, the starting opioid dose will be reduced by at least 50% in patients with risk factors or comorbidities that increase the risk of misuse, OUD or adverse reactions.
   c. Hospitalists are encouraged to reassess the need for opioid therapy frequently during hospitalization and to adjust dosage in accordance with healing, pain and functional improvement.

7. **When opioids must be used, hospitalists are encouraged to use immediate-release opioid formulations and avoid initiation of long-acting or extended-release formulations (including transdermal fentanyl) for the treatment of acute pain.**
   a. Long-acting or extended-release opioids are indicated only for the treatment of chronic pain and are not recommended for the treatment of acute or intermittent symptoms.[48]
   b. Long-acting opioids are especially dangerous in opioid-naive patients, even at recommended dosages, as they are associated with increased risk of overdose.
   c. Long-acting and extended-release opioids carry a long-term risk of dependence that is nearly 4.5 times higher than that seen with use of immediate-release formulations.[49]
   d. Use of long-acting opioids complicates the care of hospitalized patients with fluctuating renal and liver function and of patients with rapidly changing needs for pain control.
   e. Although long-acting opioids are not recommended for the treatment of acute noncancer pain in opioid-naive patients, patients on COT for pain and patients receiving MAT are frequently encountered in hospitalist practice; the recommendations for care of opioid-naive patients may not apply to the care of patients receiving COT or MAT.
   f. Discontinuation of long-acting or extended-release opioids in patients who take these medications for chronic pain or OUD treatment at the time of admission may cause opioid withdrawal and is not recommended. The baseline opioid requirements of patients receiving COT or MAT must be met prior to addressing any acute pain issues.

NOTE: Opioid products with a single ingredient (e.g., oxycodone) are favored over combination formulations (e.g., oxycodone/APAP), as patients are encouraged to take nonopioid analgesics (APAP, NSAID) consistently prior to resorting to an opioid. Use of monoproducts allows APAP or NSAID to be taken preferentially and used as a first-line agent with a lower risk of supratherapeutic dosing or accidental poisoning. Combination products are indicated by asterisk (*) below.

Short-acting opioids include but are not limited to the following agents:[37,50]

- Hydrocodone — immediate release (e.g., Vicodin*, Lorcet*, Lortab*, Norco*)
- Hydromorphone — immediate release (e.g., Dilaudid)
- Morphine — immediate release
- Oxycodone — immediate release (e.g., Percocet*, Percodan*, Roxicodone)
- Oxymorphone — immediate release (e.g., Opana)
- Tramadol — immediate release (e.g., Ultracet*, Ultram)
- Tapentadol — immediate release (e.g., Nucynta)

It is recommended that long-acting and extended-release formulations not be used for acute pain. Examples include but are not limited to the following agents:

- Fentanyl — transdermal (e.g., Duragesic)
- Hydrocodone — extended release (e.g., Hysingla ER, Zohydro ER)
- Hydromorphone – extended release (e.g., Exalgo)
- Methadone (e.g., Dolophine)
- Morphine — sustained release (e.g., MS Contin, Avinza, Kadian)
- Oxycodone — sustained release (e.g., OxyContin)
- Oxymorphone — extended release (e.g., Opana ER)
- Tramadol — extended release (e.g., Ultram ER)
- Tapentadol — extended release (e.g., Nucynta ER)

Limiting Opioid Use in the Hospital continued

8. **Hospitalists are encouraged to use the oral route of administration whenever possible. Intravenous (IV) opioids are best reserved for patients who cannot take medications by mouth, patients with suspected GI malabsorption and patients for whom immediate pain control and/or rapid dose titration is necessary.**
   a. IV opioid administration is associated with an increased risk of side effects, adverse events and medication errors.[51-53]
   b. In general, rapid onset medications have greater addictive potential. Onset with IV administration is five to 10 minutes on average compared to 15-30 minutes with oral administration.[54,55]
   c. Furthermore, the duration of action is greater with oral administration than with IV administration, which may allow for more consistent pain relief and less frequent administration.

9. **Hospitalists are encouraged to use an opioid equivalency table or calculator to understand the relative potency of different opioids when initiating opioid therapy, when changing from one route of administration to another and when changing from one opioid to another.**
   a. Most of the errors associated with preventable adverse drug events in hospitals occur at the ordering stage.[56]
   b. Clinicians may be unaware of the relative potencies of different opioids and their morphine-equivalent dose; such oversights can lead to inadvertent overdose.
   c. Clinicians may wish to consider using one of several available opioid equivalency tables or calculators — or consult with a hospital pharmacist — to better understand the relative potencies of opioids, inform starting dose calculations, guide conversions between opioids and manage different routes of administration.
   d. When changing from one opioid to another, clinicians are encouraged to reduce the dose of the new opioid by at least 25-50% of the calculated equianalgesic dose to account for interindividual variability in the response to opioids as well as the possibility of incomplete cross-tolerance.
   e. Clinicians should use extreme caution when performing conversions to and from methadone. A consultation with a hospital pharmacist or pain management specialist can help guide conversion decisions and calculations.

10. **Hospitalists are encouraged to pair opioids with scheduled nonopioid analgesic medications and to offer nonpharmacologic pain management strategies to any patient in pain.**
    a. Concurrent receipt of opioids and nonopioid analgesic medications has been demonstrated to reduce total opioid requirements and to provide more effective pain control than opioid monotherapy.[57]
    b. Hospitalists are encouraged to order nonopioid analgesics at a scheduled frequency rather than as needed to facilitate consistent administration and analgesia.
    c. Hospitalists are encouraged to be aware of contraindications and maximum dosage recommendations of nonopioid medications used in adjunct with opioid therapy.
    d. Hospitalists are encouraged to order opioid and nonopioid medications separately in order to avoid exceeding the maximum recommended dose of nonopioid analgesics contained in combination products (e.g., hydrocodone/APAP).
    e. Topical agents (e.g., lidocaine and capsaicin) and procedure-based therapies (e.g., trigger point injections, nerve blocks) can complement opioid therapy in appropriate patients.
    f. Although few studies have assessed the benefit of nonpharmacologic, non-procedure-based therapies for the treatment of acute pain in hospitalized patients, such therapies carry little to no risk, may have potential benefit and can be safely adopted. Simple nonpharmacologic therapies that are available to patients in nearly any hospital setting include music therapy, cold or hot packs, chaplain or social work visits, mindfulness training and physical therapy.[58]

Limiting Opioid Use in the Hospital continued

11. Unless contraindicated, hospitalists are encouraged to order a bowel regimen to prevent opioid-induced constipation in patients receiving opioids.

a. Constipation is a very common adverse effect of opioid therapy.
b. The limited mobility of hospitalized patients increases their risk of constipation and the use of opioids during their hospitalization amplifies this risk.
c. The administration of a bowel regimen is recommended for all hospitalized medical patients receiving opioid therapy, unless the patient is having diarrhea.
d. Given the mechanism of opioid-induced constipation, stimulant laxatives (e.g., senna, bisacodyl) are recommended as part of the bowel regimen with opioid therapy.[59]
e. Newer agents for opioid-induced constipation, including naloxegol, methylnaltrexone, alvimopan, lubiprostone and naldemedine, are efficacious but significantly more expensive and may be considered for use when conventional therapies have failed.[60] Subcutaneous methylnaltrexone was shown to be more efficacious than lubiprostone, naloxegol and oral methylnaltrexone for opioid-induced constipation.[60]
f. Osmotic laxatives (e.g., polyethylene glycol, lactulose) have demonstrated efficacy for the treatment of constipation generally but are not necessarily effective for opioid-induced constipation.
g. Due to the limited and conflicting evidence for efficacy in prevention or treatment of constipation, stool softeners are not recommended as monotherapy for opioid-induced constipation.[61]
h. Ideally, bowel movements are tracked during hospitalization and the bowel regimen modified accordingly.

12. Hospitalists are encouraged to avoid or limit, if avoidance is not possible, co-administration of opioids with barbiturates, benzodiazepines, gabapentinoids and other CNS depressants.

a. The use of any of the above agents concurrently with an opioid increases the risk of ORADEs both in and out of the hospital.
b. Patients taking opioids and benzodiazepines concurrently have 10 times the risk of fatal overdose compared with patients taking opioids alone.[62]
c. Other medications with CNS-depressant properties may also increase overdose risk including, but not limited to, nonbenzodiazepine sedative-hypnotics, muscle relaxants, sedating antidepressants, antipsychotics and antihistamines.[63-65]
d. Routine discontinuation of long-standing benzodiazepines, barbiturates and other CNS depressants is not advised due to the risk of withdrawal or worsening of the underlying condition for which these agents were prescribed. This can pose a dilemma for an inpatient provider who must order concurrent opioid therapy to control pain. In these cases, clinicians may wish to carefully consider the necessity of each medication class during hospitalization with input from the patient's outpatient providers. Clinicians are encouraged to taper the frequency and/or dose of CNS depressants when appropriate and feasible, utilizing the knowledge and assistance of a hospital pharmacist, and avoid new co-prescriptions to the extent possible, both during hospitalization and on hospital discharge.

Limiting Opioid Use in the Hospital continued

13. Hospitalists are encouraged to monitor the patient's response to opioid therapy, assess for functional improvements and recognize adverse effects.

a. Ideally, pain severity and functional status are assessed daily at a minimum.
b. An improvement in reported pain severity without an improvement in function after several days of opioid therapy may be a prompt for clinicians to reevaluate the appropriateness of ongoing opioid therapy and reconsider the etiology of the patient's pain.
c. Although hospital-specific functional measures in the setting of acute pain have not yet been validated, it is suggested that such measures be individualized based on preexisting function. Measures of function may include the ability to sit up or move in bed, move to a chair, work with physical therapy or ambulate in the hallway.
d. Protocols for the assessment for adverse effects are not well established.
e. Hospitalist clinicians are encouraged to assess for respiratory depression — the most dangerous ORADE — particularly when managing patients with sleep apnea and those receiving continuous IV opioids and/or supplemental oxygen.
    i. Because sedation typically precedes respiratory depression, it is generally suggested that patients be evaluated after each opioid dose (10-20 minutes for IV administration and 30-60 minutes for oral administration based on the time-to-peak effect).
    ii. It is not yet established whether certain patients may benefit from more intensive respiratory monitoring, such as pulse oximetry or capnography.
f. Hospitalists are encouraged to consult anesthesia or pain medicine services when managing patients with increasing opioid requirements for whom multimodal analgesic pharmacologic options have been fully implemented.

14. Hospitalists groups are encouraged to collect, track and share individual in-hospital opioid ordering patterns among their clinicians to decrease ordering variability and improve quality of care.

a. The ordering patterns of opioid medications vary among hospitalists.[26,29] Knowledge of current ordering patterns can be critical for protocol implementation, clinician education and quality improvement.
b. Tracking in-hospital opioid ordering patterns and providing comparative data to those within a practice may help reduce discrepancies and identify clinicians who can benefit from further education in multimodal analgesia and opioid stewardship.
c. This information should not be used punitively but rather to help clinicians understand their own treatment habits, facilitate change and improve care.

Prescribing at the Time of Hospital Discharge

15. Hospitalists may wish to ask patients about any existing opioid supply at home and encourage patients to safely dispose of any such supply when issuing an opioid prescription on discharge.

a. Patients may have received an opioid prescription from an outpatient clinician prior to hospitalization.
b. The PDMP database can provide information related to the potential existence of any recent prior opioid prescriptions.
c. Hospitalist clinicians are encouraged to educate patients on safe storage of opioids and to provide information on proper disposal of unused opioids (see Harm Reduction section).
d. Unused prescription opioids create the possibility of both overdose (when patients take multiple opioids concurrently, intentionally or inadvertently) and diversion, as many adults who misuse opioid prescriptions obtained their opioids from a friend or a relative.[66]

Limiting Opioid Use in the Hospital continued

16. Hospitalists are encouraged to prescribe the minimum quantity of opioids anticipated to be necessary after hospital discharge.

a. Opioid-naive patients who received opioid prescriptions upon hospital discharge are at increased risk for chronic opioid use.[67]
b. Receiving higher intensity and/or longer duration opioid therapy in the setting of acute pain has been associated with an increased risk of long-term disability and long-term opioid use.[69-71]
c. For many patients, the condition causing acute pain during hospitalization will be mostly or completely resolved by the time of hospital discharge.
d. If pain is still present at the time of discharge, often it can be adequately managed with nonopioid therapies.
e. For those with ongoing pain that is severe enough to require opioid analgesia after hospital discharge, decisions regarding the duration of therapy should be made on a case-by-case basis; generally, provision of a three- to five-day supply will be sufficient.
f. 2018 Colorado Senate Bill (SB) 18-022, Clinical Practice for Opioid Prescribing, limits first-time opioid prescriptions for acute noncancer pain to seven days, with the ability to add a discretionary second seven-day fill.[68]
g. Ideally, acute pain lasting longer than seven days after appropriate treatment of any existing underlying conditions will prompt re-evaluation of the working diagnosis and/or reconsideration of the management approach. To prescribe further opioids to the same patient, it is required by 2018 Colorado SB 18-022 that the clinician check the PDMP.[68]
h. Clinicians are encouraged to arrange an outpatient follow-up appointment for re-evaluation within seven days.

17. Hospitalist groups are strongly encouraged to collect, track and share individual discharge opioid prescribing patterns among their clinicians to decrease protocol variabilities at discharge.

a. Opioid-prescribing patterns vary among hospitalists, and knowledge of current prescribing patterns within hospitalist groups is critical for protocol implementation, clinical education and quality improvement.[26,29]
b. Tracking and comparing opioid prescribing patterns within hospitalist groups may aid in identifying clinicians who are outliers in their discharge prescribing practices. Hospitalists whose prescribing patterns vary significantly from their colleagues' prescribing patterns may benefit from further education on alternatives to opioids and how to safely decrease opioid prescription.
c. This information should not be used punitively but rather to help clinicians understand their own treatment habits and facilitate change.

18. Hospitalists are encouraged to educate patients being discharged with a prescription for an opioid about the potential for dependence and addiction associated with opioid therapy.

a. A prior history of SUD, some behavioral health disorders, use of psychotropic medications and younger age may increase this potential; however, even an opioid-naive patient with no risk factors can develop dependence and/or OUD.[72,73] When prescribing opioids, it is always appropriate to initiate a detailed discussion about the significant risk of dependence and addiction.

19. Hospitalists are encouraged to provide patients and families or caregivers information regarding how to minimize the risks of opioid therapy for themselves, their families and their communities.

a. This may include:
    i. How to take their opioids correctly (medications, doses, schedule).
    ii. Instruction to take the minimum quantity of opioid necessary to achieve tolerable levels of pain and meaningful functional improvement.
    iii. Instructions on reducing the dose and/or frequency of opioid analgesic as pain and function improve.
    iv. How to safeguard medications against diversion.
    v. How to dispose of unused medicines (see Appendix I, Resources for Patients).
    vi. Avoidance of agents that may potentiate the sedative effect of opioids, including sleeping medications, sedatives and alcohol.
    vii. Avoidance of driving or operating heavy machinery while taking opioids.
    viii. Instructions to seek help if they begin to experience any adverse effects or signs of tolerance, dependence or addiction.

Limiting Opioid Use in the Hospital continued

Policy Recommendations

1. **Improve PDMPs through interoperability and automated integration into electronic health records (EHR).**
   a. Although the Colorado PDMP is an important tool for reducing inappropriate opioid prescribing, it is cumbersome to use and often incompatible with busy hospital care workflows.
   b. Although there is no national data-sharing protocol that crosses state lines, a number of states participate in data-sharing hubs. Without data from surrounding localities, PDMPs cannot provide clinicians with the full prescribing picture. Access to nationwide data on opioid prescribing practices would enable clinicians to better detect aberrant patterns of opioid prescription and encourage their patients to seek treatment. Legislation is needed to establish a national PDMP and foster the broad exchange of prescribing information.
   c. Providers are required to use two separate logins to access their EHRs and PDMPs, a drawback that can make the use of PDMPs cumbersome and disruptive. Legislation that encourages the direct and automatic integration of PDMP data within EHRs would enable the seamless reconciliation of a patient's opioid prescription history with their current medications and health care needs.
   d. Automatic queries linked to hospital registration significantly increase the use of PDMPs in clinical decision making.[74] Systems that incorporate such technology are overwhelmingly favored by clinicians, 98-100% of whom report improved access.[75]

2. **Pain should not be considered the "fifth vital sign," and clinical medicine should move to de-emphasize numerical rating scales and incorporate functional assessments into pain management pathways.**
   a. Long promoted as the "fifth vital sign," pain has developed enormous leverage in the American medical lexicon. Medicine has overemphasized pain; as a result, physicians often feel pressured to prescribe opioids to normalize this "vital sign." In response, the American Medical Association (AMA) has issued a statement that pain should not be considered the fifth vital sign.[76]
   b. While a patient's discomfort is an important element of any clinical evaluation, it should not be given the same level of consideration as heart rate, respiratory rate, blood pressure and other objective measurements of health.
   c. While hospitalist clinicians are trained to address numerical pain ratings reflexively, pain is a complex biopsychosocial phenomenon that cannot be distilled into a one-dimensional numerical target.
   d. Numerical pain scores have been shown to increase risk of over-treatment and unintentional overdose in hospital settings.[77]
   e. Functional pain scales, which focus on a patient's ability to perform daily activities, are more clinically relevant than numerical scores and may help curtail the overtreatment of pain.

Alternatives to Opioids for the Treatment of Pain

c|h|a Colorado Hospital Association

COLORADO MEDICAL SOCIETY

COLORADO CONSORTIUM for Prescription Drug Abuse Prevention

Alternatives to Opioids for the Treatment of Pain

The CDC estimates that 20% of Americans experience chronic pain, while millions more experience acute pain on any given day. Pain affects more Americans than cancer, diabetes and heart disease combined; it is the most common reason Americans access the health care system, a leading cause of disability and a major contributor to health care costs in the United States today.[78] Despite the ubiquity of pain in medical practice, pain is poorly understood by many medical professionals and rarely taught in medical schools, 96% of which have no dedicated pain medicine module.[79] Overreliance on opioids for pain control is in part due to a poor understanding of pain and how to fully treat different pain syndromes. A better understanding of pain and the interventions that can be therapeutically applied to alleviate it is among the most important aspects of better opioid stewardship and safer, effective analgesia. Appendix XII, Understanding Pain: A Complex Biopsychosocial Phenomenon, provides a brief explanation of how clinicians are encouraged to understand pain.

Using multimodal, non-opioid medications and non-pharmacological treatments to address pain management is a proven strategy often referred to as ALTOs. The ALTO program recommends using opioids infrequently, primarily as second-line treatments and only after non-opioid alternatives have been trialed. An ALTO-based, multidisciplinary approach can transform pain management practices and result in significant benefits to patients.

Treatment Goals

- Utilize non-opioid approaches as the first-line therapy for pain.
- Utilize several agents for multimodal pain control rather than relying on monotherapies.
- Opioids can be given as rescue medication.
- Discuss realistic pain management goals with patients, emphasizing functional goals.
- Use empathic language when discussing pain.
- Discuss addiction potential and side effects with patients using opioids.
- Whenever possible, offer non-pharmacologic treatments, including distraction or comfort items (i.e., movies, music, games, massagers); education in mindfulness, guided imagery, relaxation and related psychological techniques, heat and/or ice and/or transcutaneous electrical nerve stimulation (TENS).

The ALTO program utilizes the CERTA (channels, enzymes, receptors targeted analgesia) framework to treat the physiologic components of pain. The CERTA concept optimizes the following medication classes in place of opioids: Cox-1, 2, 3 inhibitors, NMDA receptor antagonists, sodium channel blockers and GABA agonists/modulators. Specific agents include NSAIDs and acetaminophen, gabapentin, ketamine, lidocaine, antispasmodics, antidepressants and various topical agents, among others.

ALTO protocols emphasize treating the psychological and social components of pain through nonpharmacologic treatments, behavioral health referral, pharmacological treatments (when appropriate) and education. A stepwise, additive and multimodal approach is recommended in which opioids are utilized as a last resort and in combination with nonpharmacologic and ALTO medications for patients who have uncontrolled pain.

Alternative Medications and Pharmacologic Considerations

ACETAMINOPHEN

EVIDENCE: In five randomized controlled trials, acetaminophen significantly lowered pain compared to placebo without increased adverse events. Number needed to treat to achieve pain relief is four.[80]
MECHANISM OF ACTION: Not completely understood, theorized to be due to an inhibition of central prostaglandin synthesis (specifically cyclooxygenase [COX]-2) and an elevation of the pain threshold.
CONTRAINDICATIONS AND CAUTIONS: Life-threatening cases of acute hepatic failure leading to liver transplant or death have been linked with acetaminophen use. In most cases of hepatic injury, acetaminophen doses exceeded maximum daily limits and often involved the use of more than one acetaminophen-containing product.
HEPATIC DOSING: In cirrhosis with stable liver function tests (LFTs), it is recommended to reduce total daily dose to 2 g.[81]
MONITORING: Consider checking LFTs, especially if pre-existing liver disease.
DISCHARGE INSTRUCTIONS: Notify patients to avoid other over-the-counter products that contain acetaminophen and limit the total daily dose to less than 4,000 milligrams with short-term and 3,000 milligrams with long-term use.

Alternatives to Opioids for the Treatment of Pain continued

ANTIDEPRESSANTS

EVIDENCE: Duloxetine is noninferior to pregabalin for treatment of pain in patients with diabetic peripheral neuropathy.[82] Duloxetine or tricyclic antidepressants (TCA) may reduce abdominal pain and increase quality of life in patients with irritable bowel syndrome.[83] The Department of Health and Human Services 2019 Report on Pain Management and Best Practices states, "Overall, the analgesic actions of antidepressants occur even in patients who are not clinically depressed, and their analgesic effect typically occurs sooner and at lower doses than those required for the treatment of depression."
MECHANISM OF ACTION: Influence on affective components of pain. Tricyclic and serotonin-norepinephrine reuptake inhibitors (SNRIs) increase spinal cord concentrations of norepinephrine, which inhibits neuropathic pain through α2-adrenergic receptors.
OPTIONS: SNRIs (i.e., duloxetine, venlafaxine) and TCAs (i.e., amitriptyline, nortriptyline)
DOSING: Dose based on effect and tolerability. Duloxetine: start at 30 mg daily then increase to 60 mg daily after one week. Venlafaxine: start at 75 mg daily then increase by 75 mg every four days to 150–225 mg daily. Amitriptyline: start at 10 mg qhs and may titrate up to 50 mg qhs. Nortriptyline: start at 25 mg qhs and increase to 150 mg qhs. Best use in chronic pain. Do not stop abruptly. It may take up to one week or longer to take effect. Patients discharged on antidepressant therapies should have continued outpatient follow-up.
CONTRAINDICATIONS AND CAUTIONS: SNRIs and TCAs may increase suicide risk in patients 18–25 years old. Avoid TCAs in the elderly (Beers criteria) due to anticholinergic effects.
MONITORING: For SNRIs, monitor for serotonin syndrome. For TCAs, monitor QTc at baseline and periodically.

MUSCLE RELAXANTS/ANTISPASMODICS

EVIDENCE: Cyclobenzaprine reduces low back pain with a number needed to treat of three.[84] It can also reduce pain scores in patients with renal colic who are receiving NSAIDs, though the difference was not statistically significant.[85]
MECHANISM OF ACTION: Cyclobenzaprine: acts in the brainstem and reduces tonic somatic motor activity; structurally similar to tricyclic antidepressants. Tizanidine: alpha-adrenergic agonist. Methocarbamol and metaxalone: depresses CNS activity resulting in musculoskeletal relaxation. Baclofen: inhibits transmission of spinal synaptic reflexes.
ANTISPASMODIC OPTIONS: cyclobenzaprine, tizanidine, methocarbamol, metaxalone. If spasticity (not spasm), consider baclofen.
DOSING: Start at low dose and increase to effect while monitoring sedation.
CONTRAINDICATIONS AND CAUTIONS: Avoid use in elderly patients (Beers criteria) or patients at increased risk for delirium. All antispasmodics may cause sedation, but anecdotally less sedation is seen with methocarbamol. Tizanidine may cause bradycardia and/or hypotension.
DURATION OF USE: Recommended to use for shortest possible duration due to sedative side effects. Avoid abruptly discontinuing baclofen.

CAPSAICIN TOPICAL

EVIDENCE: May reduce pain in cannabis hyperemesis syndrome, arthritis and neuropathic pain. Evidence is limited.
MECHANISM OF ACTION: Causes warmth/burning sensation by binding nerve membrane receptors. Initially stimulates then desensitizes and degenerates cutaneous nociceptive neurons; substance P depletion may also reduce pain impulse transmission to the CNS.
CONTRAINDICATIONS AND CAUTIONS: May cause burning, redness or pain at the site.
DURATION OF USE: Burning should reduce with repeated administration. May take one to four weeks for maximal pain relief.

DESMOPRESSIN (DDAVP)

EVIDENCE: Desmopressin provides comparable pain relief in renal colic to opioids and even more pain relief when used concurrently with opioids. No added benefit to NSAIDs.[86]
MECHANISM OF ACTION: Proposed ureteral smooth muscle relaxation
DOSING: 0.4 mg po daily if NSAIDs are contraindicated. The intranasal formulation can be considered in patients who are unable to take pills.
CONTRAINDICATIONS AND CAUTIONS: Current or history of hyponatremia, polydipsia, von Willebrand disease. Other risk factors for hyponatremia with desmopressin use include cystic fibrosis, renal impairment, heart failure, advanced age and concomitant use of medications known to increase risk of syndrome of inappropriate antidiuretic hormone secretion (SIADH). Risk of hyponatremia is 1 in 10,000 patients.[86] IV route can be associated with higher risk of thromboembolic events.
MONITORING: Check serum sodium prior to initiation. Recheck within one week or sooner if risk for hyponatremia.

Alternatives to Opioids for the Treatment of Pain continued

DICYCLOMINE

EVIDENCE: Beneficial in irritable bowel syndrome.[87]
MECHANISM OF ACTION: Antispasmodic and anticholinergic that alleviates smooth muscle spasm of the GI tract.
CONTRAINDICATIONS AND CAUTIONS: Avoid use in elderly patients (Beers criteria) or patients at increased risk for delirium. May worsen urinary retention or ileus.

GABAPENTIN/PREGABALIN

EVIDENCE: Four out of 10 patients with neuropathy will achieve 50% pain relief with gabapentin.[88] Though more expensive, pregabalin has also been found to be effective, with better oral bioavailability and faster onset of action (one hour versus three hours with gabapentin).
MECHANISM OF ACTION: Inhibits alpha 2-delta subunit of voltage-gated calcium channels, believed to decrease conduction of neuropathic pain sensation.
DOSING: Titrate to effective dose.
CONTRAINDICATIONS AND CAUTIONS: Avoid use in older adults with a history of falls as gabapentinoids may cause syncope, impaired psychomotor function or ataxia. Concurrent use of a gabapentinoid with an opioid is not recommended due to increased risk of respiratory depression.
RENAL DOSING: Adjust dose for renal impairment.
MONITORING: Consider checking serum creatinine.
DISCHARGE: Pregabalin has misuse/abuse potential and may be cost prohibitive.

HALOPERIDOL

EVIDENCE: Reduces pain intensity and nausea scores in patients with suspected gastroparesis.[89]
MECHANISM OF ACTION: Nonselective blockade of postsynaptic dopaminergic D2 receptors, which aids with nausea. Its mechanism of action for pain reduction is not completely understood.
CONTRAINDICATIONS AND CAUTIONS: There is a higher risk of QT-interval prolongation and torsade de pointes when administered by IV route or in higher doses. Use caution if treating patients with QT-prolonging conditions, concomitant QT-prolonging drugs and underlying cardiac abnormalities. Use with caution in older adults.
MONITORING: Obtain baseline EKG and repeat periodically during therapy.

KETAMINE ORAL

Evidence: There is low quality evidence to support the use of ketamine for complex regional pain syndrome.[90] Outside the perioperative setting, most studies for acute or chronic pain treatment are small, uncontrolled and either unblinded or ineffectively blinded. Patient selection, dose and route of therapy differs across studies. Oral ketamine may have a role as add-on therapy in complex chronic pain patients if other therapeutic options have failed.[91]
MECHANISM OF ACTION: Antagonizes N-methyl-D-aspart (NMDA) receptors in the CNS.
DOSING: Average effective dose is 25–50 mg po q 4 hours prn. Do not exceed 1000 mg po over 24 hours. Injectable formulation can be used for oral administration and can be mixed with a sweet drink given its bitter taste. If concurrent opioids, lower opioid dose prior to starting ketamine to avoid respiratory depression. Ketamine has reduced oral bioavailability compared to IV administration.
CONTRAINDICATIONS AND CAUTIONS: Avoid use if seizures, psychosis, poorly controlled hypertension, heart failure, arrhythmia, increased intracranial pressure (including brain lesion, intracranial bleed), recent stroke, severe respiratory insufficiency or post-traumatic stress disorder. Ketamine can cause dose-dependent sedation.
ADVERSE EFFECTS: Hypertension, tachycardia, myocardial depression, increased intracranial pressure, vivid dreams, anxiety, hallucinations, tremors, tonic-clonic movements, nausea and sedation.
MONITORING: Ideally, vitals are checked one hour after initial oral dose, then every four hours. If acute change in vitals or intolerable psychomimetic effects, stop ketamine and consider use of benzodiazepine.
DISCHARGE: Ketamine is not recommended for routine discharge prescription. Taper ketamine prior to discharge. Ketamine is a Schedule III drug with potential for abuse.

LIDOCAINE INFUSIONS

EVIDENCE: IV lidocaine has been found safe for neuropathic pain, better than placebo and as effective as other analgesics such as morphine or gabapentin.[92] Also shown to improve pain in renal colic and critical limb ischemia compared to morphine in the ED.[93,94]
MECHANISM OF ACTION: Blocks conduction of nerve impulses through inhibition of sodium channels.
DOSING: 1 mg/kg/hr for 24 hours, then reassess therapy. Maximum recommended dose is 120 mg/hr to avoid systemic lidocaine toxicity. May use for up to 72 hours if effective and no adverse effects.

Alternatives to Opioids for the Treatment of Pain continued

CONTRAINDICATIONS: Avoid in unstable coronary disease, recent MI, heart failure, severe electrolyte disturbances, cirrhosis, arrhythmia and seizure disorders.
MONITORING: Ideally, patients are on telemetry while on a lidocaine infusion.
CAUTIONS: Local anesthetic systemic toxicity is a life-threatening adverse reaction. Early signs of lidocaine toxicity include circumoral numbness, metallic taste in mouth, dizziness, light-headedness or tinnitus. Later signs of toxicity include confusion, slurred speech, blurred vision, myoclonic jerking and seizures. If ongoing undetected or untreated toxicity, can progress to coma, respiratory arrest and cardiovascular effects (hypotension, pulse rate <50 or >120, cardiac arrest). If concerned, stop lidocaine and consider poison center consult and lipid emulsion. It is recommended that a lipid rescue kit be made readily available in any area of practice that utilizes IV lidocaine.
ADVERSE REACTIONS: Recommended duration of use is 24 hours. Longer durations of therapy can be considered but have increased risk of toxicity.

LIDOCAINE TOPICAL

EVIDENCE: In myofascial pain, lidocaine patches decrease reported pain compared to placebo.[95]
MECHANISM OF ACTION: Blocks conduction of nerve impulses through inhibition of sodium channels.
OPTIONS: Patch, ointment, cream, viscous and jelly. Concentrations vary. Can use up to three patches at one time. A small study suggests that it is safe to administer for 24 hours at a time (versus remove after 12 hours) on healthy subjects with intact skin.[96]
CONTRAINDICATIONS AND CAUTIONS: Only recommended for use on intact skin.
DISCHARGE: If 5% prescription concentration is cost prohibitive, can prescribe lidocaine 4%, which is available over the counter.

MENTHOL TOPICAL

EVIDENCE: Methyl salicylate and menthol provide significant pain relief of muscle strain compared to placebo.[97] In a small study, menthol was more effective than ice.[98]
MECHANISM OF ACTION: Stimulates receptors producing cold sensation.
CONTRAINDICATIONS AND CAUTIONS: Recommend for use on intact skin.

NON-STEROIDAL ANTI-INFLAMMATORIES (NSAIDS)

EVIDENCE: When combined with acetaminophen, can reduce acute pain by 50% in seven out of 10 patients.[99] Adding an NSAID to a pain regimen containing an opioid may have an opioid-sparing effect of 20%–35%.[100] For renal colic, both opioids and NSAIDs lead to clinically relevant reduction in pain scores but opioids have higher rates of adverse reactions, particularly vomiting.[39]
MECHANISM OF ACTION: Inhibits proinflammatory prostaglandin production via inhibition of COX-1 and COX-2 enzymes.
OPTIONS: Ibuprofen, naproxen, ketorolac, diclofenac, indomethacin and selective COX-2 inhibitors meloxicam, celecoxib.
DIFFERENT SIDE EFFECT PROFILES: In general, COX-2 selective NSAIDs have a lower risk of GI side effects but a higher risk of cardiac side effects. Non-selective NSAIDs have a lower risk of cardiac side effects but a higher risk of GI side effects.
CONTRAINDICATIONS AND CAUTIONS: NSAIDs increase the risk of myocardial infarction and stroke. Contraindicated in the setting of recent coronary artery bypass graft surgery or myocardial infarction. Can also cause increased risk for GI adverse events including bleeding, ulceration and perforation of the stomach or intestines. Risk is especially increased in elderly (Beers criteria) and in patients with prior peptic ulcer disease or GI bleeding. Caution should also be used in patients on concomitant anticoagulants or antiplatelet agents. Avoid use in patients with chronic kidney disease, cirrhosis or heart failure. Risk of renal injury is higher in patients who are elderly, dehydrated or with other comorbidities including heart failure, diabetes and cirrhosis.
SPECIAL CONSIDERATIONS: Ketorolac should ideally be limited to five days given GI risks. Also, limit ketorolac to 15 mg q 6 hours if age >65, weight <50 kg or moderately elevated serum creatinine.
MONITORING: Check serum creatinine and discuss history of GI ulceration prior to initiation.
RECOMMENDED DURATION OF USE: Use the lowest effective dose for the shortest possible duration.

(TABLE 4)

Risk of Gastric Ulcer Bleeding with NSAIDs[101]

Individual NSAID	Adjusted conditional RR (95% CI)
Low	
Celecoxib	1.0 (0.4-2.1)
Ibuprofen	4.1 (3.1-5.3)
Naproxen	7.3 (4.7-11.4)
Indomethacin	9.0 (3.9-20.7)
High	
Ketorolac	14.4 (5.2-39.9)

SOURCE: American College of Gastroenterology Guidelines, 2009[102,103]

(TABLE 5)

GI Risk Factor Assessment and NSAID Therapy

GI risk factor assessment	Treatment
High Risk	
• History of previously complicated ulcer, especially recent • OR more than two risk factors: 1) Age >65 years, 2) high dose NSAID therapy, 3) previous history of uncomplicated ulcer or 4) concurrent use of aspirin, corticosteroids or anticoagulants	Alternative therapy or COX-2 inhibitor + PPI
Moderate Risk (one or two risk factors)	NSAID + PPI
Low Risk (no risk factors)	NSAID alone

SOURCE: American College of Gastroenterology Guidelines, 2009[102,103]

TOPICAL NSAIDs

EVIDENCE: To achieve 50% reduction in musculoskeletal pain, number needed to treat was 3.7 for topical diclofenac topic solutions, which is similar to that for oral NSAIDs.[104] Only about 5% of topical NSAIDs are systemically absorbed compared to oral NSAIDs but studies show there is local absorption into tissues and synovium.[105] Consider use in patients who have relative contraindications to oral NSAIDs.
MECHANISM OF ACTION: Inhibits proinflammatory prostaglandin production via inhibition of COX-1 and COX-2 enzymes.
OPTIONS: Diclofenac gel, patch and solution.
CONTRAINDICATIONS: Similar side effect profile to oral NSAIDs; however, a meta-analysis showed systemic adverse events were uncommon and did not differ from placebo.[105]
DISCHARGE: More expensive than oral NSAIDs.

Alternatives to Opioids for the Treatment of Pain continued

TAMSULOSIN

EVIDENCE: Moderate- or low-quality evidence that it may reduce the time to stone passage and use of pain medications. Sub-analysis shows that benefit might be best for stones 6 mm or larger. Tamsulosin does not influence the need for surgery.[106]

MECHANISM OF ACTION: Alpha-1 receptor antagonist, produces smooth muscle relaxation.

CONTRAINDICATIONS AND CAUTIONS: May cause orthostatic hypotension, complications with cataract surgery and abnormal ejaculation.

DURATION OF USE: Until stone passage.

Practice Recommendations

1. All inpatient hospitalist groups are encouraged to implement ALTO programs and utilize opioid-sparing pain treatment pathways when treating appropriate patients with the following conditions:
   a. Pleuritic pain
   b. Abdominal pain
   c. Musculoskeletal pain
   d. Extremity pain
   e. Renal colic
2. Hospitalist groups should consider integrating ALTO treatment strategies and pathways into their computerized physician order entry systems to facilitate seamless adoption by clinicians.
3. For the types of pain represented in the five treatment pathways below, a combination of scheduled acetaminophen and an NSAID is considered first-line therapy unless contraindicated.
4. In all types of pain, non-pharmacologic options (i.e., distraction and comfort items, ice, heating pad, therapeutic mobility and positional adjustments) are recommended for concomitant use with pharmacologic options.
5. For musculoskeletal pain, consider a multimodal treatment approach using scheduled acetaminophen and an NSAID, a muscle relaxant and topical medications.
6. For pleuritic pain, consider use of a multimodal treatment approach that includes the administration of scheduled acetaminophen and an NSAID and lidocaine topical patches. Consider regional anesthetic interventions when appropriate.
7. For pain with a neuropathic component, consider use of a gabapentinoid and/or topical or IV lidocaine in addition to scheduled acetaminophen and an NSAID.
8. For pain caused by renal colic, consider use of scheduled acetaminophen and an NSAID, desmopressin, lidocaine infusion and/or tamsulosin.
9. For abdominal pain, etiology should guide the selection of pharmaceutical agents. All patients are encouraged to ambulate and use a heating pad.
10. For extremity pain, use scheduled acetaminophen and an NSAID as well as gabapentin and topical lidocaine patches if neuropathy is present.
11. Duloxetine may be considered for add-on therapy in patients with chronic neuropathic, musculoskeletal or abdominal pain who are receiving other first-line therapies.
12. When feasible and appropriate, transitioning IV medications to oral therapies maximizes therapeutic duration and facilitates transition to outpatient care.
13. Ideally, outpatient prescribing will use nonopioid multimodal medications first and reserve opioids for use as rescue medications.
14. It is recommended that admitted patients receiving outpatient chronic opioid therapy have their medication continued, if appropriate, after confirming use and dosage with the PDMP and/or their primary care providers.
15. ALTO protocols may not be appropriate for patients on hospice, with sickle cell crisis, burn or cancer-related pain.

Alternatives to Opioids for the Treatment of Pain continued

Treatment Pathways

The following are suggested pain treatment pathways for commonly encountered conditions.

PLEURITIC PAIN

For pneumonia, pulmonary embolism, inflammatory pleurisy or uncomplicated rib fracture

FIRST LINE THERAPY:

- Heating pad
- Hold pillow during splinting
- Ibuprofen 400–600 mg PO Q 6 hr*
- Acetaminophen 1000 mg PO TID
- Lidocaine 5% topical patches 1–3 TD daily

SECOND LINE THERAPY:

- Ketorolac 15 mg IV Q 6 hr x 5 days max as alternative to oral NSAID*
- Consultation for regional anesthetic interventions (nerve blocks, epidural, etc.) if rib fracture with refractory pain and/or risk of respiratory deterioration.

EXTREMITY PAIN

For cellulitis, deep vein thrombosis or neuropathy

FIRST LINE THERAPY:

- Elevate the extremity if appropriate
- Acetaminophen 1000 mg PO TID
- Ibuprofen 400–600 mg PO Q 6 hr*
- Gabapentin 100–300 mg PO 1-3x daily
- Lidocaine 5% topical patches 1–3 TD daily if localized pain with intact skin

SECOND LINE THERAPY:

- Ketorolac 15 mg IV Q 6 hr x 5 days max as alternative to oral NSAID*
- Lidocaine 1 mg/kg/hr IV infusion over 24 hours if severe neuropathy or ischemia
- If chronic neuropathy, consider adding duloxetine 30 mg PO daily.

ABDOMINAL PAIN

For non-pregnant patients without a GI bleed, perforation or obstruction. Suspected etiology should guide appropriate pain treatment.

FIRST LINE THERAPY:

- Heating pad
- Bowel regimen if constipation
- Ambulation
- Acetaminophen 1000 mg PO/PR TID
- Famotidine 20 mg IV BID
- Simethicone 80 mg PO QID
- Carafate 1 g PO AC and QHS
- Ketorolac 15 mg IV Q 6 hr x 5 days max*
- Ondansetron 4 mg IV/PO Q 6 hr PRN, prochlorperazine 5 mg IV/PO Q 6 hr PRN or metoclopramide 5 mg IV/PO Q 6 hr PRN if nausea

SECOND LINE THERAPY:

- Haloperidol 1–2 mg IV/PO Q 4 hr PRN if uncontrolled nausea
- Dicyclomine 10–20 mg IM/PO TID
- Capsaicin 0.075% topical cream TID
- If chronic pain, add duloxetine 30 mg PO daily or amitriptyline 10 mg PO QHS. Consider outpatient pain psychology or pain specialist referral.

**Evaluate gastric ulcer risk prior to starting NSAIDs, especially if on concomitant therapeutic anticoagulation.*

Alternatives to Opioids for the Treatment of Pain continued

MUSCULOSKELETAL PAIN

For joint/arthritis and muscular/myofascial pain

FIRST LINE THERAPY:

- Heating pad or ice
- Menthol topical cream QID
- Acetaminophen 1000 mg PO TID plus
- Ibuprofen 400–600 mg PO Q 6 hr*
- Cyclobenzaprine 5 mg PO TID
- Therapeutic mobility and exercise; PT or OT consult if pain is limiting function

SECOND LINE THERAPY:

- Ketorolac 15 mg IV Q 6 hr x 5 days max as alternative to oral NSAID*
- Lidocaine 5% topical patches 1–3 TD daily
- Diclofenac 1% gel 2–4 g Q 8 hr if not on IV or PO NSAIDs
- Gabapentin 100–300 mg PO 1-3x daily
- If chronic pain, add duloxetine 30 mg PO daily. Consider outpatient pain psychology or pain specialist referral.
- Consider specialty consult for septic and/or acute autoimmune arthritis.

THIRD LINE THERAPY:

- Ketamine 25–50 mg PO Q 8 hr PRN for complex regional pain syndrome after failing opioid therapy

RENAL COLIC

For nephrolithiasis pain

FIRST LINE THERAPY:

- Heating pad or ice
- Ketorolac 15 mg IV Q 6 hr x 5 days max*
- Acetaminophen 1000 mg PO TID

SECOND LINE THERAPY:

- Cyclobenzaprine 5 mg PO TID
- Tamsulosin 0.4 mg PO daily until stone passage
- Lidocaine 1 mg/kg/hr IV infusion over 24 hours
- Desmopressin 0.4 mg PO daily when NSAIDs are contraindicated

**Evaluate gastric ulcer risk prior to starting NSAIDs, especially if on concomitant therapeutic anticoagulation.*

Harm Reduction

c|h|a Colorado Hospital Association

COLORADO MEDICAL SOCIETY

COLORADO CONSORTIUM for Prescription Drug Abuse Prevention

Harm Reduction

Harm reduction is a set of practical strategies and ideas aimed at reducing the negative consequences associated with illicit drug use. The harm reduction approach is predicated on respecting patients and their choices, removing stigma and meeting patients "where they are" without judgment. In an ideal world, patients would be compelled to stop using illicit drugs by logical physician counseling. The simplistic directive to "stop using because you may die or be hurt" is ineffective and often damaging to the physician-patient relationship. Clinicians best serve patients who use illicit substances by building patient trust, which can be accomplished with a harm reduction approach.

Initially developed in response to the U.S. AIDS epidemic, the harm reduction philosophy has been used in recent years to guide the care of people who inject drugs (PWID); its principles are broadly applicable to most patients with SUD. Injection drug use is intertwined with the opioid epidemic. The use of illicit and IV drugs has increased commensurate with the rise in opioid prescriptions, as roughly 75% of injection heroin addictions originate with prescription opioid misuse.[107]

Harm reduction aims to prevent infectious complications of IV drug use (IVDU), including HIV/AIDS, hepatitis B and C, sepsis and endocarditis. It reduces the risk of overdose and other drug-related fatalities. It also decreases the other negative effects drug use may have on individuals and communities. Many patients who present with opioid-related health concerns, including withdrawal, overdose and injection-related infections, are not ready to begin treatment on the day they visit the hospital. Clinicians support these patients best by carefully and compassionately counseling them to adopt practices that will reduce risk of harm until the time they are ready to seek addiction treatment.

High Stakes: The Risks of IV Drug Use and Infectious Complications

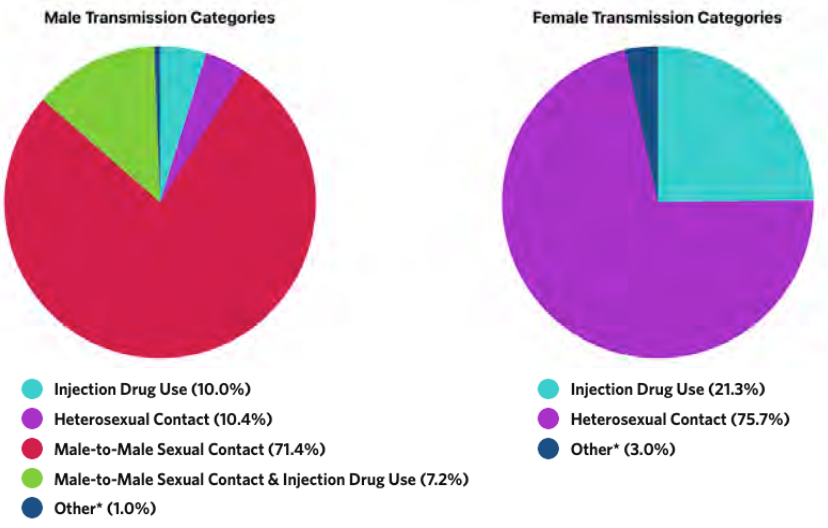
HIV

In 2016, injection drug use directly accounted for 9% of new HIV diagnoses, 13% of new AIDS diagnoses and is believed to have contributed to approximately 20% of new HIV/AIDs diagnoses.[108] In Colorado, 24% of new HIV diagnoses in women and 5% in men are associated with injection drug use **(FIGURE 4)**.

(FIGURE 4)

Colorado: Estimated Percentage of Male vs. Female with New HIV Diagnosis

People Living with HIV, by Transmission Category, 2016

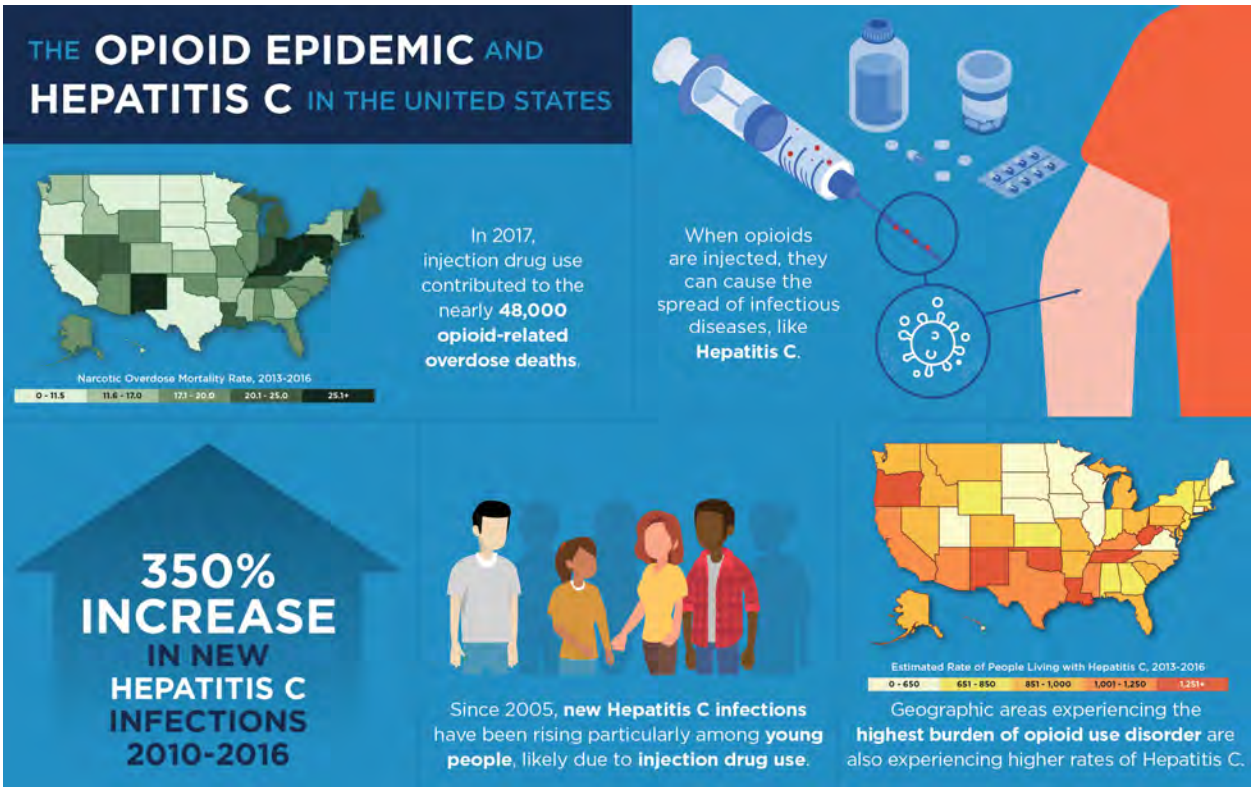


**Includes risk factor not reported or identified, along with hemophilia, blood transfusion, perinatal exposure, or missing/suppressed data*

SOURCE: AIDSVu[109]

(FIGURE 5)

The Opioid Epidemic and Hepatitis C in the United States



SOURCE: HEPVu[115]

HEPATITIS B AND C

Injection drug use accounts for the majority of new hepatitis C (HCV) infections.[110] Acute HCV infections have increased about 3.5-fold since 2010.[111] Of the 1,371 cases of hepatitis B reported in 2016, more than 34.4% of cases indicated the use of injection drugs.[112] In Colorado, the age-adjusted HCV rate has increased by 129% since 2012, primarily due to IVDU; 894 new cases were reported in 2016 alone.[113]

As hospitalist clinicians are aware, hepatitis B and C infections place patients at high risk for developing cirrhosis, liver failure and hepatocellular carcinoma. Hepatitis C is curable with new medications such as sofosbuvir or combination medications such as ledipasvir/sofosbuvir. However, these treatments often cost more than $80,000 per regimen, placing significant strain on medical systems and payers.[114]

ENDOCARDITIS

Rates of bacterial endocarditis, once a rare infectious disease, are soaring across the country. The overall incidence of acute bacterial endocarditis is hundreds to thousands of times higher among PWID compared to the non-IVDU population (150-2,000 cases/100,000 person-years versus 1.7-6.2 cases/100,000 person years).[116] Cases of infectious endocarditis are increasing in association with the current opioid epidemic and affect young white, non-Hispanic people from rural areas the most.[117-119] A CDC report from North Carolina found that the incidence of hospitalizations for endocarditis among drug-dependent patients has increased 12-fold from 2010 to 2015, and associated health care costs increased 18-fold.[120] Similar increases are occurring in Colorado, where Centura Health's hospital system reported an increase in IVDU-related endocarditis from four cases in 2012 to 66 cases in 2017.[121] Endocarditis places significant strain on patients, health systems and payers. A 2017 CDC report found that, on average, cost of endocarditis-related hospitalizations between 2010 and 2015 exceeded $50,000 and 42% of hospitalized patients were on Medicaid or without insurance.[120]

Harm Reduction continued

INVASIVE BACTERIAL INFECTIONS

Soft tissue infections and more serious necrotizing soft tissue infections are common complications of IVDU. One California-based study found that of 169 PWID, 32% developed injection-related cellulitis or abscess.[122] More significant infections such as wound botulism, osteomyelitis, epidural abscess, necrotizing fasciitis and invasive methicillin-resistant Staphylococcus aureus (MRSA) have all been linked to IV drug use. A 2018 CDC report found that PWID were 16.3 times more likely to develop invasive MRSA infections than non-IVDU. In the same CDC report, invasive MRSA infections from IVDU increased from 4.1% of invasive MRSA cases to 9.2% from 2011 to 2016.[123]

Bacterial infections are a common reason for PWID to seek medical care and represent a significant burden to the health care system. One study estimated the cost of serious bacterial infections related to IVDU at $700 million per year in 2012.[117] As rates of IVDU increase, so do the economic burdens and the toll on community health.

(FIGURE 6)

MRSA: A Threat to People Who Inject Drugs

SOURCE: CDC MMWR[123]

Harm Reduction continued

STIGMA AND BIAS AS OBSTACLES TO HEALTH CARE

SUD is defined by genetic predisposition and long-term changes in brain structure and function. Patients often suffer from uncontrollable, compulsive drug cravings that render them powerless, even in the face of catastrophic social and health-related consequences.[125] Health care providers have been shown to view patients with SUD negatively and to behave in a manner toward them that erodes both clinician empathy and patient care.[124] As a result, patients with OUD who inject drugs often go to great lengths to avoid medical care and frequently sign out against medical advice before treatment is complete. It is imperative that clinicians make the hospital setting a welcoming and safe place for those who seek care. The Harm Reduction Action Center (HRAC), Colorado's largest syringe access program, provides education, social support and limited medical services to PWID. Based on years of experience providing care to patients with OUD, HRAC has compiled best practices for providing patient-centered care to patients with OUD and PWID to address the stigma these patients face **(TABLE 6)**.

It is important to recognize the behavioral health contributors to SUD and the frequent comorbidities of pain, anxiety and depression. Successful management of the behavioral health comorbidities and the social and medical needs of patients with SUD often requires clinicians to aid patients in accessing ongoing care from several clinical specialties. This process can be successfully supported by compassionate rather than punitive approaches. Motivational interviewing techniques, cognitive behavioral therapy (CBT), dialectical behavioral therapy and other counseling methods have been shown to be effective for some patients, particularly when paired with appropriate MAT and a collaborative harm reduction-minded approach.[126-128]

(TABLE 6)

Best Practices for the Treatment of PWIDs

- Assume drug users care about their health. It is not uncommon for clinicians to assume that drug users don't care about their health; such misperceptions are noticed by patients. Fearing negativity and condescension, many drug users avoid seeking health care and attempt to "doctor" themselves.
- Respect the patient at all times. Patients often overhear health care providers talking about them negatively outside of the room or behind a curtain. Assuming the patient can't hear them, clinicians can be heard labeling patients as a "druggie" or "drug seeker."
- Treat the patient's pain. Some providers automatically undertreat or minimize pain when they suspect drug-seeking behavior in order to "teach the patient a lesson" or for fear of "feeding their addiction."
- Ask the patient's permission to include new or additional team members if they are not part of the primary team. Health care providers occasionally bring in other colleagues to observe patients without their permission. Insensitive "look at the crazy thing this junkie did to herself/himself" remarks veiled as "learning experiences" are inappropriate and promote a feeling of shame in the patient.
- Contacting authorities to report illegal substance use is a violation of patient privacy and the Health Insurance Portability and Accountability Act (HIPAA). If law enforcement needs to be contacted, (e.g., a mandatory reporting of assault with a deadly weapon), advise the patient of that plan.
- Discharge planning should be conducted with the patient to avoid vague or unrealistic aftercare plans. Addressing non-medical needs can promote improved adherence to medical treatment.
- Provide medically accurate, targeted educational information about risk reduction rather than judgmental speeches or shaming lectures about drug use.

Harm Reduction continued

Evidence-based harm reduction strategies, rather than fear- and stigma-driven ultimatums, improve patient and community outcomes.[129] Providing effective care for PWID requires a significant investment of time, effort and specialized knowledge. For providers who are unable to provide the degree of time, effort or knowledge these patients require, additional resources and support can be mobilized to meet the patient's needs. These resources are listed in the "Referral and Treatment" section.

Harm reduction and therapeutic relationship-building are especially critical in communities where buprenorphine and methadone treatment programs are scarce and/or plagued by long waiting lists. Hospitalists are encouraged to gain familiarity with harm reduction principles, learn to perform effective interventions and access the education and resources needed to integrate harm reduction into their practices.

Practice Recommendations

1. **Patients with OUD should be managed without judgment; addiction is a medical condition, not a moral failing. Ideally, caregivers will endeavor to meet patients "where they are," infusing empathy and understanding into the patient-provider relationship. Behavioral changes can be encouraged with understanding and patience, incorporating patients' own motivations and goals.**
   a. Hospitalist clinicians are encouraged to seek out educational opportunities to better understand addiction and the stigma associated with OUD.
   b. A harm reduction approach should incorporate the following principles:
      i. Humanism: Seek to accept and understand patients without moral judgments.
      ii. Pragmatism: Target messaging toward harms and concerns over health rather than moral/societal standards; abstinence is an ideal and not prioritized.
      iii. Individualism: See the patient as an individual.
      iv. Autonomy: Respect the patient's decisions.
      v. Incrementalism: Small, step-by-step improvements may open the door to further treatment and recovery.
      vi. Accountability without termination: Patients are responsible for their choices and behaviors. While this may at times go against medical advice, termination of the relationship can cause the patient harm.
   c. Counsel patients and allow them to seek treatment — or not — at their own pace **(TABLE 7)**. Pressuring or forcing patients into treatment for SUD is usually ineffective, violates patient autonomy and creates an adversarial rather than therapeutic relationship.

(TABLE 7)

Counseling Patients with Addiction

DO	DON'T
• Use respectful language when discussing the patient's drug use. • Assess the patient's readiness to change. • Respect the patient's decisions regarding treatment. • Encourage patients to be honest with providers about any drug use. • Make information available that is specific, medically accurate and relevant to the needs of the patient.	• Don't use negative terminology such as "addict" or "junkie." • Don't tell the patient they are "ruining their life" or are "going to die." • Don't attempt to pressure the patient to begin treatment for SUD. • Don't make assumptions about the mental or physical health of patients with OUD. • Don't let the stigma associated with injection drug use affect how a patient is treated.

Harm Reduction continued

2. **Hospital-based clinicians are encouraged to be knowledgeable about how to prevent overdose in PWID and to counsel patients on safe practices prior to discharge. Patients should be counseled to:**
   a. Avoid using alone.
      i. Overdoses that occur when patients use opioids alone often result in death.
      ii. Encourage drug users to inject in the presence of others. Colorado's Good Samaritan laws protect individuals who call 911 to report an overdose, exempting both them and the overdose victim from arrest and prosecution for minor drug charges.
   b. Always carry naloxone.
      i. Naloxone is safe and effective both in and out of the hospital. Since 1996, the opioid reversal agent has reversed more than 26,000 overdoses.[130]
      ii. Because most overdoses are witnessed and transpire over hours, naloxone is patients' most powerful tool for preventing overdose death.
      iii. Numerous studies over the past 20 years have confirmed that lay people can administer naloxone out of hospital with therapeutic success.[130-134]
      iv. Consider dispensing naloxone in the hospital to any patient with known or suspected IV drug use, and encourage at-risk patients to keep naloxone within reach at all times.
   c. If injecting heroin or fentanyl, first inject a small dose to assess potency.
      i. Variations in drug potency are common, especially with the popular practice of cutting or substituting heroin with fentanyl or carfentanil.
      ii. When trying a new product, encourage patients to use a small dose (i.e., test shot) to gauge its potency.
   d. Do not mix opioids with alcohol, benzodiazepines, barbiturates or other sedating drugs.
   e. Do not go back to using the same dose after a period of abstinence, which often occurs after hospitalization, incarceration or a period of sobriety.
   f. Consider using fentanyl test strips. Fentanyl test strips have been recommended by some organizations as a method to identify heroin that is laced with fentanyl or fentanyl analogues. Hospitalist clinicians should consider the prevalence of illicit fentanyl in their communities and advise patients about the utility and availability of fentanyl test strips as appropriate.

3. **Hospitalists are encouraged to be familiar with safe injection practices for heroin and other intravenous drugs so that they can effectively communicate with patients about their drug use practices and inquire about potentially unsafe habits.**
   a. As the HIV epidemic challenged clinicians to be knowledgeable and to inquire about patient sexual preference and sexual behaviors and to counsel patients on safe and unsafe sexual practices, the opioid epidemic requires providers to be knowledgeable about IV drug use and common unsafe practices in PWID.
   b. Heroin is inexpensive and widely available. Patients addicted to prescription opioids often turn to heroin for economic reasons or for its faster and more intense high.
   c. Though all heroin is derived from morphine, it is processed and sold in several forms. Pure heroin is a white powder that can be snorted or smoked; it is often "cut" with sugar, starch, powdered milk or quinine and dominates in markets east of the Mississippi River. West of the Mississippi, "black tar" heroin predominates. The dark color of this sticky or hard form of heroin is due to impurities from crude processing. Black tar heroin must be dissolved, diluted and injected in order to be effective in generating a high or withdrawal relief.
   d. Heroin is often mixed with fentanyl and fentanyl analogues, increasing potency and risk of overdose. Some advocate for fentanyl test strips as a harm reduction technique, although there is no consensus on their broad use.
   e. The vast majority of medical professionals are unfamiliar with drug injection methods and are ill prepared to discuss safeguards with PWID. Clinicians are encouraged to be familiar with the equipment used to inject heroin and IV drugs (APPENDIX II). Clinicians may wish to familiarize themselves with the steps to injecting drugs, including what common and/or unsafe practices are associated with each step and how to mitigate risk (APPENDIX III).
   f. Most IV drug users learn from their peers and often learn dangerous habits. It is important for clinicians to be able to engage patients, identify unsafe practices and educate patients.

Fentanyl Testing Strips

Fentanyl is an opioid medication that is 50-100 times more potent than morphine.[135] A significant amount of heroin has been found to contain some amount of fentanyl. A recent study of 242 heroin users in British Columbia, Canada, found that 29% of study participants had urine samples that tested positive for fentanyl and 73% of the users did not know they were using fentanyl.[136] This inadvertent use of fentanyl by many heroin users has contributed to the rise in overdoses seen in the United States and Colorado.

Many drug users report concern regarding the uncertain presence of fentanyl in their drugs, and even more indicate a desire to know if their drugs contain fentanyl.[137] Certain harm reduction initiatives advocate for the off-label use of fentanyl testing strips (e.g., BTNX fentanyl testing strips) by drug users prior to injecting heroin. The majority of drug users report that knowing if their drugs contain fentanyl would alter their behavior associated with drug use, specifically using "test shots" or seeking out non-fentanyl containing drugs.

BTNX fentanyl testing strips were found to have the highest sensitivity and specificity as well as the lowest detection threshold of fentanyl testing technologies evaluated. The sensitivity was between 96-100% and the specificity was between 90-98%.[137] BTNX can detect other fentanyl analogues including carfentanil, acetylfentanyl, butyrylfentanyl, 3-methylfentanyl, ocfentanil and sufentanil.[138]

Despite positive initial studies, there is still a need for more definitive data surrounding the off-label use of fentanyl testing strips by users of heroin and other illicit substances.

At this time, CO's CURE leadership and participating organizations take no position on the use of fentanyl testing strips as part of hospital-based harm reduction initiatives.

4. **Hospital-based clinicians are encouraged to be knowledgeable about and counsel patients on how to prevent communicable diseases such as HIV and hepatitis B and C in PWID. Ideally, patients would be tested for viral diseases and offered or referred to treatment as appropriate prior to discharge.**
   a. Data collected by the HRAC estimates that 24% of the PWID they serve are hepatitis C-positive; injection drug use is the leading transmission method of this pathogen in the United States.
   b. A notorious HIV outbreak in one small Indiana town is a cautionary tale about what can happen when safe injection practices are ignored. The community of Austin, Indiana (population 4,000) was ravaged by the virus in 2015 when 235 new cases were diagnosed — all attributed to a local epidemic of injection oxymorphone use.[139]
   c. Avoid sharing equipment.
      i. Although HIV can survive only minutes outside the body, it can live for days to weeks inside hollow-bore needles.
      ii. The risk of transmission is highest when drug paraphernalia is shared between multiple users within a short period of time.
      iii. Hepatitis B and C are particularly virulent and can survive between one and three weeks outside of the body.
      iv. These pathogens can be spread easily via injection equipment (e.g., needles, syringes, cookers [spoons], injection water and cotton), as shown in Appendix II.
      v. Patients can obtain new equipment for free through local syringe access programs (formerly referred to as needle exchange programs).

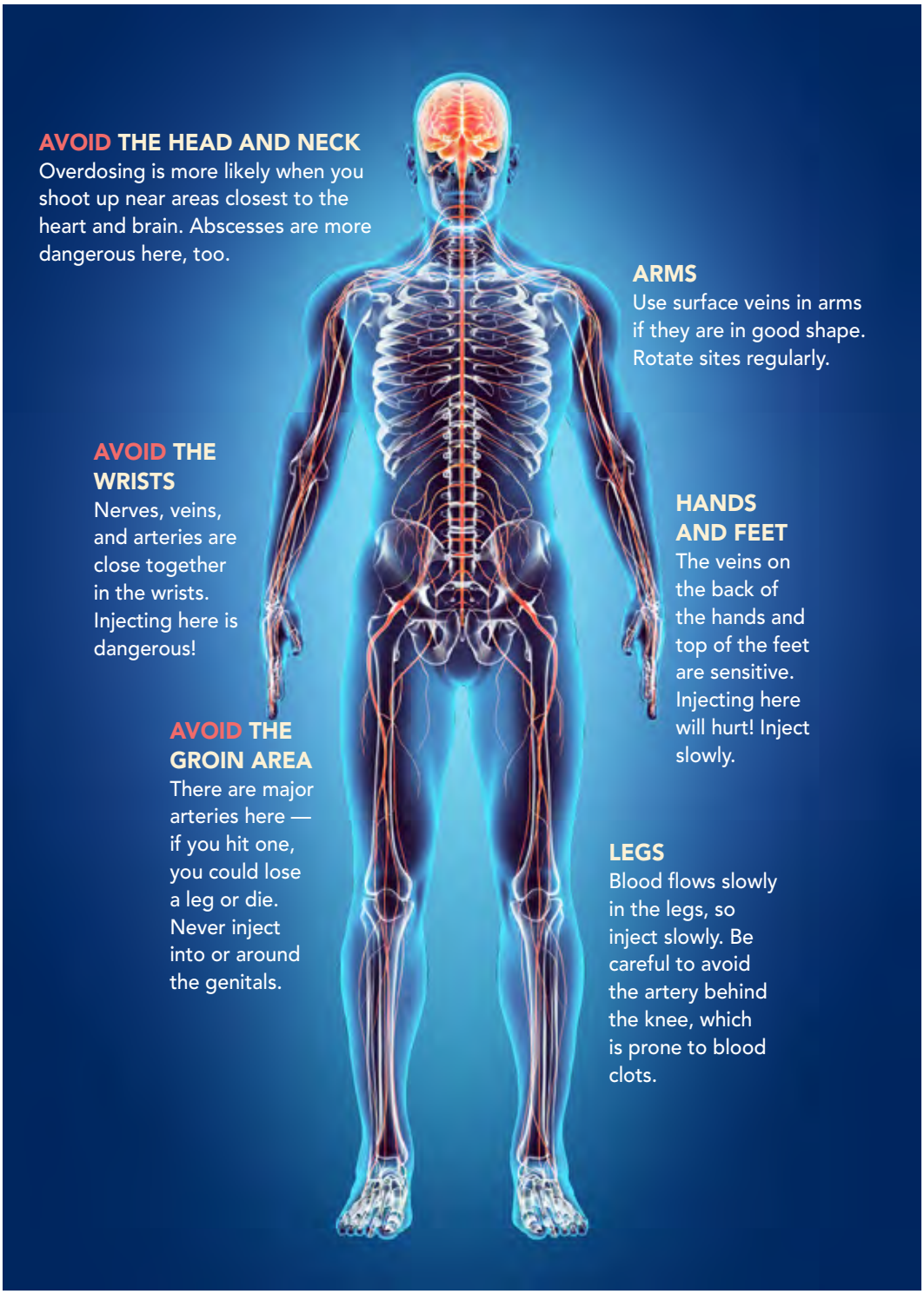
d. As a last resort, if a patient must reuse equipment, it should be cleaned thoroughly with full-strength bleach. Syringes and needles both should be actively cleaned then rinsed.
e. Materials should be rinsed and soaked for at least two minutes but optimally 10 minutes. The longer materials soak, the greater the chance of killing viral pathogens and the safer they are to reuse. All materials should be rinsed with clean cold water afterward.

5. **Hospital-based clinicians are encouraged to be knowledgeable about how to prevent soft tissue infections and serious invasive bacterial infections in PWID. Ideally, patients would be counseled on safe injection practices prior to discharge.**
   a. Practice good hygiene.
      i. Always encourage hand washing and cleansing of the injection site.
      ii. Recommend the use of alcohol pads to sterilize skin prior to injection.
   b. Use sterile equipment.
      i. Reusing equipment increases the risk of bacterial contamination. Patients can obtain new equipment for free through local syringe access programs (formerly referred to as needle exchange programs). If such resources are unavailable, advise patients to purchase needles, syringes and alcohol pads at pharmacies.
      ii. As a last resort, if a patient must reuse equipment, it should be cleaned with full-strength bleach.
      iii. Materials should be rinsed and soaked for at least two minutes but optimally 10 minutes. The longer materials soak, the greater the chance of killing viral pathogens and the safer they are to reuse. All materials should be rinsed with cold clean water afterward.
      iv. The average heroin injection drug user injects three to five times per day.
   c. Use sterile water to prepare the product.
      i. Many infections stem from unsafe water supplies; some users report using river water, toilet water or saliva to dissolve product into an injectable form.
      ii. Bottled water is NOT sterile. If a patient has drunk from a water bottle prior to use, it is contaminated and poses a high infection risk.
      iii. Optimally, patients will have access to single-use containers of sterile water.
      iv. If these are unavailable, water should be sterilized by heating it at a rolling boil for 10 minutes and allowing it to cool.
   d. Avoid "skin popping" or "muscling," where heroin or drugs are not injected into the vein but into subcutaneous tissue or muscles. This predisposes users to abscesses and soft tissue infections.

6. **Hospital-based clinicians are encouraged to be knowledgeable about how to prevent vein sclerosis and preserve veins in PWID. Ideally, patients would be counseled on safe practices prior to discharge.**
   a. Patients should be advised to use the smallest (highest gauge) needle possible; rotate injection sites, starting distally.
   b. Patients should be encouraged to drink water to remain well hydrated.
   c. Patients are encouraged to use citric acid if an acidic solution is required to dissolve product (use of lime, lemon or orange juice should be discouraged, as these are more sclerotic and carry a higher risk of infection).
   d. Advise against using the jugular, femoral or pedal veins, which can further increase the danger of infection **(FIGURE 8)**.
   e. *The Guide to Getting Off Right* is a good resource for safe injection practices written by and for PWID, with medical advisors involved.

(FIGURE 8)

Safer Injecting for Patients



SOURCE: 2017 Colorado ACEP Opioid Prescribing & Treatment Guidelines

Harm Reduction continued

7. **Ideally, all hospital patients who receive prescriptions for opioids and those who have been diagnosed with SUD or a related medical issue will be educated on the dangers of polysubstance use.**
    a. Polysubstance use in patients with SUD is extremely common, and education on adverse outcomes with the concurrent use of stimulants and other psychoactive substances is recommended.
        i. Using multiple unmeasured, potentially toxic substances can be very dangerous. If abstinence is not an option, precautions against overdose, prevention of infection and protecting veins as discussed above are recommended.
        ii. Proper hydration, including replacement of electrolytes, is extremely important, particularly with stimulants. Stimulants often predispose to heat stroke — proper recognition, cooling and resting can help prevent this complication.
        iii. Stimulants will increase tolerance toward other sedating agents. This contributes to increased toxicity and the potential for overdose. Hence, use of "speed balls" (heroin with cocaine) and "goofballs" (heroin with methamphetamine) should be discouraged.
        iv. Substances such as cannabis, hallucinogens and dissociatives can lead to uncomfortable altered states of consciousness, paranoia, psychosis, anxiety and panic attacks, among other complications. Counsel patients to seek medical attention if these occur.
8. **Hospitalists are encouraged to offer an inpatient addiction medicine consultation to every hospitalized patient who injects drugs. Consultation with behavioral health clinicians and social work as appropriate and available may also be of benefit to patients.**
    a. Treatment of underlying SUD is the most direct way to assure a patient's long-term health.
    b. Addiction medicine clinicians are trained to help patients access care for SUD, initiate MAT where appropriate, educate patients on MAT and aid transition to MAT and other addiction medicine care once a patient leaves the hospital.
9. **Ideally, all patients who use IV drugs will be referred to local syringe access programs upon discharge, where they can obtain sterile injection materials and support services such as counseling, HIV/hepatitis testing and treatment referrals.**
    a. Syringe access programs have demonstrated cost-effectiveness in reducing HIV transmission and prevalence.[140]
    b. The additional resources these centers often provide (e.g., sterile water, cooking units and cleaning solutions) can help reduce harm.
    c. The World Health Organization (WHO) says there is a "compelling case that needle and syringe programs substantially and cost effectively reduce the spread of HIV among IV drug users and do so without evidence of exacerbating injecting drug use at either the individual or societal level."[141]
    d. In 2000, the AMA adopted a position strongly supporting the efficacy of these programs when combined with addiction counseling.[142]
    e. An online list of local syringe access/harm reduction programs can be found through the North American Syringe Exchange Network (**APPENDIX IV**, Map and Listing of Syringe Access Programs in Colorado [Updated March 2020]).

Harm Reduction continued

10. Hospital-based clinicians are encouraged to work with hospitals to establish take-home naloxone programs to provide high-risk patients with naloxone and overdose education at discharge. If naloxone cannot be given at time of release, clinicians are encouraged to inform patients about the over-the-counter availability of the drug in most Colorado pharmacies. Clinicians may also prescribe naloxone, though a prescription is not necessary.

a. In April 2018, the U.S. Office of the Surgeon General issued an advisory urging health care systems to increase access to naloxone, joining the WHO, CDC and AMA in advocating for wider availability of naloxone.
   i. The advisory states, "For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an OUD, and community members who come into contact with people at risk for opioid overdose, knowing how to use naloxone and keeping it within reach can save a life."[143]

b. A 2018 national survey by the American Psychiatric Association found that nearly one in three people report knowing someone who is or has been addicted to opioids.[144]

c. PWID have contact with other people at risk. While patients who have been given naloxone will rarely rescue themselves, they can often use naloxone to rescue others who have overdosed.

d. Clinicians are encouraged to counsel family members and friends on recognizing overdose and using naloxone.

e. The risk of opioid overdose is widespread; the antidote is not. Despite their effectiveness, take-home naloxone programs are present in fewer than 10% of U.S. counties and only 12% of counties with the highest opioid overdose rates.[145]

(TABLE 8)

Criteria for Naloxone Direct Distribution or Prescription

Consider directly dispensing or prescribing naloxone to the following high-risk patients at discharge:

- Receiving care for opioid intoxication or overdose
- Have suspected substance abuse or nonmedical opioid use
- Are taking >100 mg morphine equivalents per day
- Are receiving an opioid prescription for pain PLUS:
  - A prescription for methadone or buprenorphine
  - A history of acute or chronic pulmonary disease
  - A history of renal dysfunction, hepatic disease or cardiac comorbidities
  - Known or suspected excessive alcohol use or dependency
  - Concurrent use of benzodiazepines or other sedatives
  - Known or suspected poorly controlled depression
- Are taking opioids but have unreliable access to emergency medical services
- Have been recently incarcerated and released from prison
- Have resumed opioid use after a period of abstinence

Pharmacies that participate in Colorado's standing naloxone protocols can be found at *www.stoptheclockcolorado.org*

Harm Reduction continued

11. Hospitalists are encouraged to be familiar with Colorado's regulations pertaining to naloxone. State laws eliminate liability risk for prescribing the drug, encourage Good Samaritan reporting of overdose and make naloxone legal and readily available over the counter in most pharmacies.

a. Colorado State-Specific Policy Summaries Third-Party Naloxone Bill (Colorado SB 13-014). Passed in 2013, the bill removes the following:
   i. Civil liability for prescribers
   ii. Criminal liability for prescribers
   iii. Civil liability for layperson administration
   iv. Criminal liability for layperson administration

b. Colorado 911 Good Samaritan Law (Colorado Revised Statutes [CRS] §18-1-711) and Immunity When Overdoses Reported (2016 Colorado HB 16-1390):
   i. Protects a Samaritan acting in good faith
   ii. Ensures no arrest or prosecution for possession
   iii. Ensures no arrest or prosecution for paraphernalia and protection from other crimes

c. Standing Orders for Naloxone (2015 Colorado SB 15-053): Any medical professional with prescriptive authority can write a standing order for naloxone that can be dispensed by other designated individuals (such as pharmacists and harm reduction organizations).
   i. Find participating pharmacies at www.stoptheclockcolorado.org.
   ii. With these standing orders, pharmacists and harm reduction organizations can now provide naloxone to any person who requests it. Those who might particularly benefit from having naloxone include:
      1. A family member, friend or other person in a position to assist a person at risk of overdose.
      2. An employee or volunteer of a harm reduction organization.
      3. A first responder.
      4. An individual at risk of overdose.

d. Additional Resources

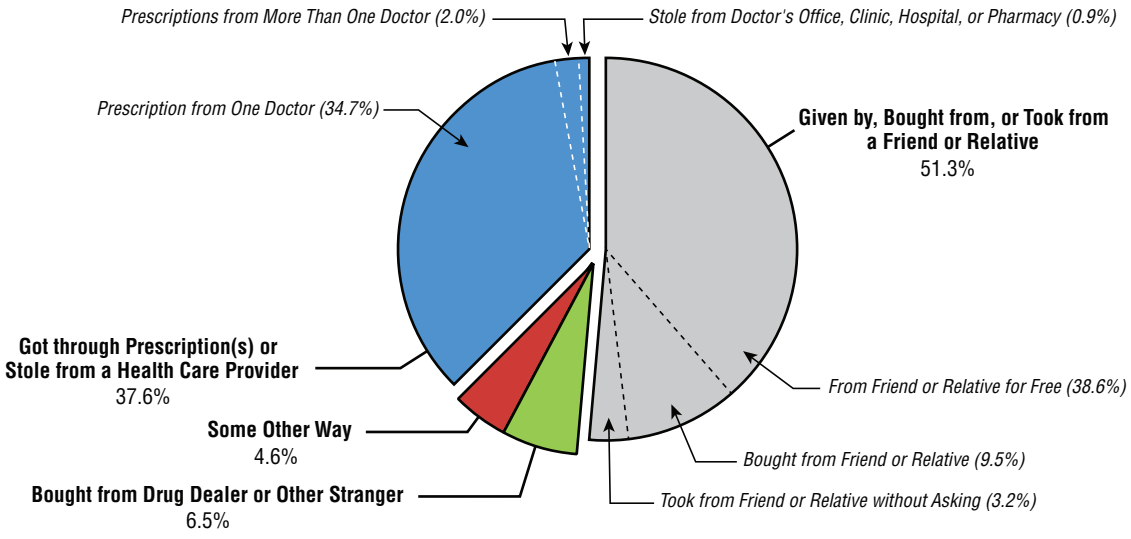
12. Ideally, all hospital patients who receive a prescription for an opioid are educated on their risks, safe storage methods and the proper disposal of unused medications.

a. Most patients who misuse opioids obtain them from friends or family.

b. Prescriptions should be stored safely, out of view and, ideally, in a locked location. Diversion of opioids by adolescents poses a significant risk.

c. Once the acute pain phase has ended and medication is no longer required, it is critical that patients promptly dispose of unused opioids.

9.9.Million People Aged 12 or Older Who Misused Pain Relievers in the Past Year



SOURCE: Substance Abuse and Mental Health Services Administration 2019 – Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health

d. If disposing of the medication at home, patients can be instructed to:
   i. Remove the medication from its original container and remove any labels or cross out identifying information.
   ii. Mix the pills with something that can't be eaten (e.g., cat litter, coffee grounds, sawdust, home cleanser, etc.).
   iii. Place the mixture in a sealable bag, empty can or other durable container that prevents leakage.
   iv. Wrap the container in newspaper or a plain brown bag to conceal its contents. Place it in the trash the day of collection.
   v. The FDA allows opioids to be flushed down the toilet; however, more environmentally friendly disposal methods are encouraged.[146]
e. An increasing number of communities also offer prescription take-back programs. Patients are encouraged to utilize one of the preferred disposal locations found on www.takemedsback.org or participate in a national DEA-sponsored take-back event. More than half of the counties in Colorado offer safe disposal sites for controlled substances and the number of these facilities is increasing rapidly.
   i. Additional Resources:
      1. www.takemedsseriously.org
      2. www.corxconsortium.org/wp-content/uploads/Safe-Disposal-Brochure.pdf
      3. www.deadiversion.usdoj.gov/drug_disposal/takeback/index.html

Policy Recommendations

1. **Ensure wider public access to harm reduction agencies and community programs that provide resources for PWID.**
   a. The passage of CRS §25-1-520 in 2010 legalized the establishment of syringe access programs with local jurisdiction approval.
   b. Community programs providing needle exchange and disposal services, sterile equipment, free counseling and HIV/hepatitis screening are cost-effective strategies for preventing the transmission of bloodborne pathogens.
   c. Ideally, these programs, many of which also provide basic medical and social services to this high-risk population, would be well funded and expanded beyond their current levels.

2. **When local programs are unavailable for PWID, hospitals should consider establishing their own programs to provide services such as syringe exchanges.**
   a. 2019 Colorado SB 19-227 allows for syringe access out of hospitals and EDs and limits liability of such programs.
   b. This recommendation is especially applicable to rural communities, which are particularly vulnerable to communicable disease outbreaks and are unlikely to have local syringe access programs.
   c. Hospitalists in these environments have an opportunity to intervene when caring for high-risk patients.
   d. Hospitals can partner with their local health departments and state and federal authorities to establish programs that encourage harm reduction.
   e. Ideally, such initiatives would be funded by national, state or local governments, nonprofit organizations and/or grants to make these services cost-effective for participating hospitals.

Treatment of Opioid Use Disorders (OUD)

c|h|a
Colorado Hospital Association

COLORADO
MEDICAL SOCIETY

COLORADO
CONSORTIUM
for Prescription Drug Abuse Prevention

Treatment of Opioid Use Disorder (OUD)

In 2018, an estimated 21.2 million people (approximately 1 in 13) required treatment for substance use disorder; however, only a small minority received care.[147] The consequences of this treatment gap are substantial, including dramatically increased risks of overdose injury and death, transmission of HIV, viral hepatitis, invasive bacterial infections and a range of risky behaviors. Medicine now recognizes that OUD is a chronic, relapsing medical illness. Like patients with other chronic illnesses, patients diagnosed with OUD need ongoing comprehensive, evidence-based care. Abstinence-oriented treatments are ineffective for the treatment of OUD, with relapse rates of greater than 80%.[148] The gold standard for treatment of OUD employs one of the three FDA-approved medications: methadone, buprenorphine or naltrexone. It is important to recognize that opioid dependence and opioid addiction are different conditions; patients may be physically dependent on buprenorphine or methadone, but when maintained on these medications, the risks and behaviors seen in addiction are avoided. People receiving MAT can lead fulfilling, productive lives while maintained on medication.

Overwhelming evidence demonstrates that patients receiving MAT have lower morbidity and mortality, higher treatment retention rates, lower rates of opioid-related hospital admissions and lower rates of readmission.[149] As many hospitalists are aware, a quarter or more of patients with OUD will leave the hospital against medical advice due to craving, withdrawal, social pressures and fear of stigma or mistreatment.[150] Patients whose withdrawal is managed with buprenorphine or methadone are less likely to leave against medical advice and have shorter, less complicated admissions.[151-152] Finally, patients with OUD have been shown to have a decreased risk of overdose death following a hospitalization during which they received opioid agonist treatment.[153]

Hospitalists are ideally positioned to help people with untreated OUD by screening patients consistently and offering treatment to patients with OUD in a non-stigmatizing, compassionate manner. The stigma surrounding OUD leads some patients to conceal their disease, while past negative experiences with the health care system make other patients wary of medical providers. Hospitalists working today have an opportunity to radically change how this patient population is treated. They can ensure that patients on buprenorphine or methadone are maintained on their medication while hospitalized. As important, hospitalist practices can establish practices and protocols so that any patient who wants to initiate MAT can do so while hospitalized. By adopting these approaches, hospital-based clinicians can make an enormous contribution to improving the lives of people with OUD.

Practice Recommendations

1. **Hospitalists are encouraged to identify, diagnose and treat patients with OUD. MAT with buprenorphine, methadone or naltrexone is the evidence-based treatment for OUD.**
   a. OUD and SUD more generally are poorly understood by many medical professionals. The gap in knowledge begins in medical school, where SUD is insufficiently addressed. Despite the fact that overdose is the leading cause of death in Americans under the age of 50, as of 2018 fewer than 10% of medical schools had a formal addiction curriculum.[154]
   b. Many medical professionals fail to recognize the distinction between dependence and addiction. Addiction includes both physiologic dependence on a substance and the behaviors that surround the use of that substance. These behaviors include the 4 C's of addiction: loss of Control, use despite negative Consequences, Compulsive use and Cravings.
   c. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines OUD by the 11 criteria listed in **TABLE 9**. Of note, physiologic dependence represents only two of the 11 criteria used to diagnose OUD.

Treatment of Opioid Use Disorders (OUD) continued

(TABLE 9)

Summarized DSM-5 Diagnostic Categories and Criteria for Opioid Use Disorder

CATEGORY	
Impaired Control	• Opioids used in larger amounts or for longer than intended • Unsuccessful efforts or desire to cut back or control opioid use • Excessive amount of time spent obtaining, using or recovering from opioids • Craving to use opioids
Social Impairment	• Failure to fulfill major role obligations at work, school, or home as a result of recurrent opioid use • Persistent or recurrent social or interpersonal problems that are exacerbated by opioids or continued use of opioids despite these problems • Reduced or given up important social, occupational, or recreational activities because of opioid use
Risky Use	• Opioid use in physically hazardous situations • Continued opioid use despite knowledge of persistent physical or psychological problem that is likely caused by opioid use
Pharmacological Properties	• Tolerance as demonstrated by increased amounts of opioids needed to achieve desire effect; Diminished effect with continued use of the same amount • Withdrawal as demonstrated by symptoms of opioid withdrawal syndrome; opioids taken to relive or avoid withdrawal

SOURCE: Psychiatric Times, DSM-5[155]

d. In order to be diagnosed with OUD, a patient must meet two of the 11 criteria within a 12-month period. Two to three criteria indicates mild OUD, four to five criteria indicates moderate OUD and six to seven indicates severe OUD. Persons who are prescribed opioids for chronic pain often exhibit pharmacological tolerance and dependence but would not necessarily be considered to have OUD.
e. Most patients with OUD are not adequately treated. As of 2019, the Colorado Department of Human Services, Office of Behavioral Health estimates a treatment gap of approximately 70%, with only 30% of patients with OUD receiving treatment.
f. MAT using buprenorphine, methadone or naltrexone is the cornerstone of the treatment of OUD. A Cochrane review found the addition of counseling to medication conferred no added benefit; MAT plays a central, not adjunctive, role in the treatment of OUD.[156]
g. MAT is not "substituting one addiction for another." While patients may continue to have a physiologic dependence on buprenorphine or methadone, they do not exhibit the behavioral hallmarks of addiction. MAT substitutes dependence for addiction and, in doing so, decreases morbidity and mortality while improving quality of life.
h. Abstinence-based therapies are largely ineffective for the treatment of OUD. Ideally, hospitalists would not recommend abstinence-based treatments for OUD.[157]
i. Like many of the conditions hospitalists encounter, OUD is a chronic, relapsing disease. Just as hospitalists treat the underlying disease of a diabetic admitted with neuropathy, ideally, patients admitted with complications of OUD would be treated for OUD.
j. Ideally, patient education about OUD would be provided during hospital admission. Patients with OUD benefit from learning that OUD is a chronic disease in which brain function and structure are altered. Analogies with other chronic diseases like diabetes may help providers communicate the idea that OUD is a chronic disease in which biochemical derangements, behavior and medication contribute to disease management and recovery.

Treatment of Opioid Use Disorders (OUD) continued

k. Patients with OUD who do not wish to initiate MAT should know that opioid agonist therapy will make them feel more comfortable while hospitalized and reduce their risk of overdose upon discharge.
l. OUD is a chronic, relapsing disease for which most patients require ongoing treatment. Opioid agonist treatment for OUD can be maintained for years or be a lifelong drug. Clinicians are encouraged to tell patients to anticipate long-term treatment. Patients on appropriate therapeutic doses of methadone or buprenorphine are cognitively normal and function normally in society.
m. Ideally, buprenorphine or methadone treatment will not be prematurely tapered. Premature or rapid tapers of buprenorphine or methadone increase the risk of relapse.
n. Hospitalist clinicians are encouraged to coordinate management of MAT with a pain or addiction specialist and/or the patient's primary care provider.
o. Patients and providers can be educated that relapse in OUD is common, manageable and not a contraindication to future trials of treatment.

2. Hospitalists are encouraged to screen all patients for OUD and SUD more generally.

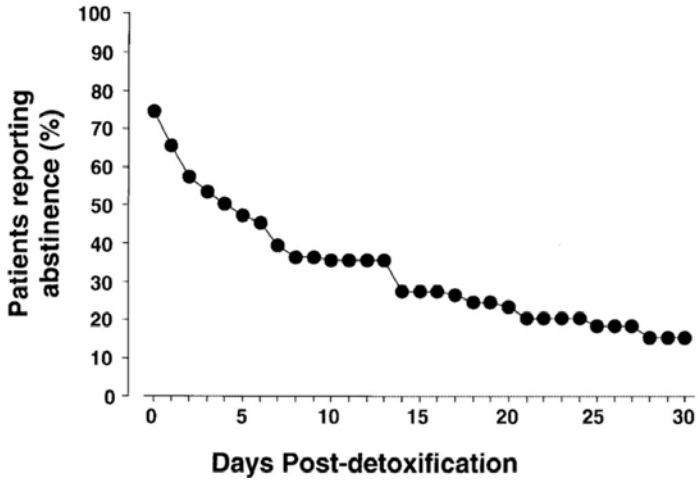
a. While some patients present with a clear diagnosis of OUD, many patients with OUD will conceal their disease.
    i. Between 8-29% of hospitalized patients are estimated to have a non-alcohol SUD, but only 64% of these patients are identified as having SUD by their hospital treatment teams.[158] The stigma surrounding OUD and SUD prevents many patients from providing a full, accurate history.
b. Hospitalist clinicians are encouraged to consider using the Screening, Brief Intervention and Referral to Treatment (SBIRT) protocol to identify and address risk for substance misuse and SUD in all patients.
    i. Properly documented SBIRT is reimbursed by private and public insurers. The screening component of an SBIRT protocol can be any validated screening instrument. Colorado SBIRT is an excellent resource for clinicians.
    ii. OUD is defined by the DSM-5 and replaces "opioid addiction" and "opioid dependence" as a diagnostic entity. Some clinicians report that reviewing the DSM-5 diagnostic criteria for OUD with a patient can be helpful **(TABLE 9)**.
    iii. When OUD is suspected, an opioid-specific screening tool like the Rapid Opioid Dependence Screen (RODS) can be used to further evaluate for OUD. The RODS can be administered and scored in two to three minutes. **(SEE APPENDIX V)**
    iv. A non-stigmatizing, medically accurate, empathic approach to the patient interview is most effective in eliciting an accurate substance use history.
    v. The principles and techniques of motivational interviewing can be powerful tools when engaging with patients with SUD. More information about motivational interviewing can be accessed HERE.
c. Laboratory data, medical records and the PDMP are not reliable predictors of OUD.
    i. Some opioids will not be detected on routine urine toxicology. Urine screening can detect metabolites of morphine and heroin within three days of last use and sometimes longer in chronic users. False-negative tests may occur because not all opioids are detected on routine urine screening with immunoassays. Use of synthetic opioids (oxycodone, hydrocodone, hydromorphone, fentanyl, tramadol) will rarely produce a positive result for opioids and will require specific screening. False positive tests can be seen in patients ingesting poppy seeds or taking medications such as quinolones and rifampin.
    ii. Clinicians should be aware that many patients with OUD will not be flagged by the PDMP. Among non-medical users of opioids, over 70% acquire opioids from friends, family or illicit purchase.[159]

Treatment of Opioid Use Disorders (OUD) continued

3. **"Detox" and abstinence-oriented therapies are ineffective for the treatment of OUD, and hospitalist clinicians are encouraged to educate patients, families and caregivers on the high failure rates of these therapies.**
   a. The neurophysiology of opioid dependence is such that willpower is rarely sufficient to override craving for opioids in moderate to severe OUD or to tolerate opioid withdrawal.
   b. Abstinence-oriented treatments are dangerous and ineffective for the treatment of OUD, as they increase the risk of overdose when patients relapse. Relapse rates are greater than 80% when treatment is abstinence-based.[167-168]
   c. If abstinence is desired by the patient, it is best to achieve this over the course of months or years and through a very slow and cautious tapering process. It is still unknown if discontinuation is an appropriate goal as several studies show relapse rates consistently surpassing 50% at one month after discontinuation of buprenorphine maintenance therapy.[169-171]
   d. A study of IV opioid users comparing detoxification versus buprenorphine treatment highlights the potential harms of abstinence and detoxification-related care versus MAT. In this cohort, 0% of patients who underwent abstinence-based therapy remained in treatment for over 90 days, and 20% died. In contrast, in the group of patients receiving buprenorphine, 75% remained in treatment at one year, and no patient died.[168]

(FIGURE 9)

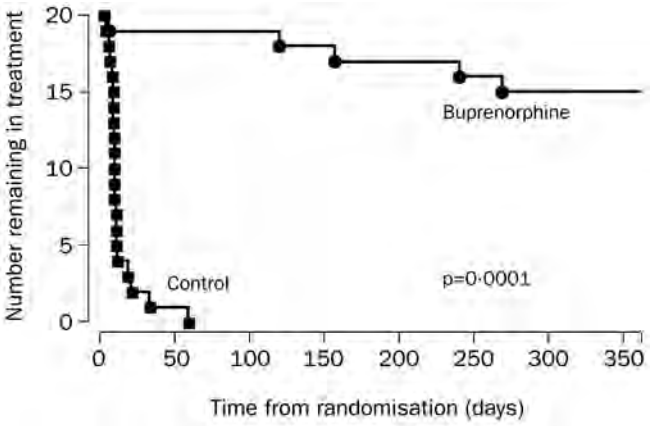
Inpatient Opioid Detoxification Outcomes (Heroin)



SOURCE: Chutuape et al. Am J Drug Alcohol Abuse. 2001 Feb;27(1):19-44.[172]

(FIGURE 10)

One-Year Retention Detox vs Buprenorphine Maintenance



SOURCE: Lancet [168]

Treatment of Opioid Use Disorders (OUD) continued

e. Hospitalists are encouraged to counsel patients who want to pursue an abstinence-based approach of the increased failure and overdose rates, point out evidence that MAT is more efficacious and work to address potential misconceptions or stigma around MAT.

4. **It is recommended that hospitalized patients with untreated OUD be offered MAT with either buprenorphine or methadone and that appropriate patients are initiated on MAT during hospitalization.**
   a. Methadone, buprenorphine and naltrexone are the three FDA-approved medications for the treatment OUD. Methadone is a full opioid agonist and buprenorphine is a partial agonist. Methadone and buprenorphine are termed opioid agonist treatment (OAT) to distinguish them from naltrexone, which is a full opioid antagonist.

(TABLE 10)

Characteristics of Medications for Treatment of OUD

CHARACTERISTIC	METHADONE	BUPRENORPHINE	NALTREXONE
Brand Names	Dolophine, Methadose	Subutex, Suboxone, Zubsolv	Depade, ReVia, Vivitrol
Class	Agonist (fully activates opioid receptors)	Partial agonist (activates opioid receptors but produces a diminished response even with full occupancy)	Antagonist (blocks the opioid receptors and interferes with the rewarding and analgesic effects of opioids)
Use and effects	Taken once per day orally to reduce opioid cravings and withdrawal symptoms	Taken orally or sublingually (usually once a day) to relieve opioid cravings and withdrawal symptoms	Taken orally or by injection to diminish the reinforcing effects of opioids (potentially extinguishing the association between conditioned stimuli and opioid use)
Advantages	High strength and efficacy as long as oral dosing (which slows brain uptake and reduces euphoria) is adhered to; excellent option for patients who have no response to other medications	Eligible to be prescribed by certified physicians, which eliminates the need to visit specialized treatment clinics and thus widens availability	Not addictive or sedating and does not result in physical dependence; a recently approved depot injection formulation, Vivitrol, eliminates need for daily dosing
Disadvantages	Mostly available through approved outpatient treatment programs, which patients must visit daily	Subutex has measurable abuse liability; Subozone diminishes this risk by including nalxone, an antagonist that induces withdrawal if the drug is injected	Poor patient compliance (but Vivitrol should improve compliance); initiation requires attaining prolonged (e.g. 7-day) abstinence, during which withdrawal, relapse, and early dropout may occur

SOURCE: NEJM[160]

Treatment of Opioid Use Disorders (OUD) continued

b. Hospitalists are ideally positioned to treat patients with OUD. Hospitalized patients with OUD may be particularly receptive to initiating treatment for OUD. When admitted for opioid-related illnesses, fear of bad outcomes as well as forced abstinence may prompt consideration of the benefits of treatment. Sixty-seven percent of hospitalized patients with SUD report a desire to cut back or stop using and 44% of patients with OUD report a strong desire to receive MAT.[158]
c. Hospitalized patients receiving MAT have higher treatment retention rates, lower rates of opioid-related hospital admissions, lower rates of readmission and lower risks of opioid overdose upon discharge.[149, 152] In addition, patients in untreated opioid withdrawal may experience autonomic dysregulation that exacerbates their condition and complicates their care.
d. Treatment with buprenorphine or methadone significantly reduces all-cause mortality and opioid-related mortality and morbidity.[163, 164]
e. Patients not interested in long-term MAT will still benefit from OAT during hospitalization to reduce craving and withdrawal symptoms. Furthermore, patients who initially refuse MAT may be more receptive to treatment after their withdrawal symptoms are controlled.
f. For hospitalists initiating treatment of OUD, buprenorphine and methadone are preferred over naltrexone. Buprenorphine and methadone are easier to initiate, offer better treatment retention rates[161] and have more evidence supporting their use. **TABLE 11** offers a comparison of methadone and buprenorphine.
g. The choice of opioid agonist should be a shared decision with the patient. Buprenorphine can be dispensed in primary care settings, unlike methadone, which requires referral to federally licensed programs.
h. In many communities, treatment with buprenorphine is easier to access for patients after discharge. It is easy to transition from buprenorphine to methadone in the outpatient realm, whereas transitioning from methadone to buprenorphine poses significant challenges because of the risk of precipitated withdrawal. These factors, as well as buprenorphine's superior safety profile, make it the first-line treatment for OUD in hospital settings.
i. Before initiating buprenorphine, patients must be in opioid withdrawal. Patients should have a Clinical Opioid Withdrawal Score (COWS) of at least eight before buprenorphine induction **(APPENDIX VI)**. If patients are initiated on buprenorphine prematurely, they may experience severe precipitated withdrawal. Some patients may have prior negative experience with precipitated withdrawal. A careful, collaborative history and clinical assessment decreases the risk of precipitated withdrawal.
j. Management of precipitated withdrawal usually involves dosing with additional buprenorphine and adjunctive medications. Failing that, treatment of precipitated withdrawal with a full opioid agonist with strong affinity for the mu receptor may be appropriate.

Treatment of Opioid Use Disorders (OUD) continued

(TABLE 11)

A Comparison of Methadone and Buprenorphine

	METHADONE	BUPRENORPHINE
Mechanism	Full opioid agonist	Partial opioid agonist, usually paired with naloxone (opioid antagonist)
Patients for whom should use caution or avoid	Allergy, severe liver disease, QTc prolongation, drug-drug interactions, high-risk job	Allergy, severe liver disease, heavy EtOH or benzo, need for acute opioids, recent methodone
Risk of withdrawal when starting medication	None	Some, if not in withdrawal prior to starting may have precipitated withdrawal
Side effects/risks	Hypogonadism, Torsades, constipation, sweating	GI upset, constipation, headache, insomnia
Sedation/respiratory depression	At high doses in non-tolerant patients or slow metabolizers has protential for sedation, worse in combination with some medications	Ceiling effect for respiratory depression therefore less risky (unless concurrent use of sedating drugs, e.g., alcohol/ benzodiazepines)
Overdose risk from opioid replacement	Low-moderate, higher when initiating treatment or in combo with other medications	Low, increased by concurrent sedating medications
Retention in treatment	Higher in methadone, with possible contribution from increased structure of programs	May be slightly lower than methadone, retention improves at doses over 16 mg
Visit frequency	Daily visits to maintenance treatment program, take-homes may be allowed if stable for long term. This structure helps some patients, some dislike it.	Can range from daily to monthly depending on patient treatment needs, may be provided in primary care setting. Also available in some methdone clinics, increasing structure and decreasing diversion risk.
Diversion potential	Low for directly observed therapy (DOT), high for take home	Low for DOT, moderate for take-homes, reduced by co-formulation with naloxone
Who can prescribe after discharge?	Opioid treatment program only	Any physician, NP, or PA who has been trained and possesses DATA2000 waivers (aka X-number)
Mortality	Both options substantially decrease all-cause mortality over no treatment, methadone may have higher mortality but may be confounded	Both options substantially decrease all-cause mortality over no treatment, buprenorphine may have lower mortality but may be confounded

Some patients may decline buprenorphine or methadone, but still be interested in medication assisted treatment. In these cases, one option is naltrexone, however it has been shown to have very high drop-out rates so is not considered first line. Naltrexone can only be started after a patient has completely withdrawn from opioids – roughly 5-7 days for short acting and 7-10 days for long acting. One option is to give naloxone as a trial before administering naltrexone, to make sure the patient doesn't experience precipitated withdrawal. Dosing usually begins with 25mg on the first day, and is then is increased to 50mg daily. For IM formulation, the dose is usually 380mg q4 weeks. The most common side effects are nausea, vomiting, and headache.

SOURCE: Project SHOUT[162]

Treatment of Opioid Use Disorders (OUD) continued

5. **Hospitalists are encouraged to maintain hospitalized patients already receiving buprenorphine or methadone on their MAT regimens.**
   a. It is recommended that all patients receiving MAT are continued on their medication when admitted, whether in the setting of acute pain, chronic pain or possible surgical intervention. Continuing these medications improves pain control, reduces the use of opioid analgesia[165] and reduces the risk of relapse post discharge.[166]
   b. Discontinuing opioid agonist treatment complicates clinical assessment and treatment, risks putting patients into withdrawal, increases the chance patients will leave against medical advice and requires a patient to re-start treatment on discharge.
   c. Rare situations where clinicians may wish to consider modifying dosage or holding medications include:
      i. Severe sedation or respiratory depression
         1. If not sedated but receiving additional sedating medications, monitor closely but do not withhold OUD medications.
      ii. QTc>500 on methadone
         1. Acute illness and new medications can change QTc and elevate risk. Consider decreasing dose of QTc-prolonging medications, including methadone, if QTc is prolonged.
      iii. Newly decompensated liver disease.
      iv. Interactions with medications that have significant drug interactions with methadone.
         1. Methadone dose may require adjustment. Clinicians are encouraged to consult a clinical pharmacist for a more complete list of interactions.
            a. Drugs that may increase methadone concentration or effect include azole antifungals, some SSRIs, tricyclic antidepressants, erythromycin, ciprofloxacin and quetiapine. If using these medications, closely monitor for sedation and unintentional overdose and consider use of alternative medications if possible.
            b. Drugs that may decrease methadone concentration include rifampin, many antiretrovirals, phenytoin and carbamazepine. If using these medications, closely monitor for opioid withdrawal and consider use of alternative medications if possible.
   d. Providers are encouraged to verify a patient's dose with their office-based opioid treatment (OBOT) or opioid treatment program (OTP) provider.
      i. Outpatient pharmacy, the Colorado PDMP system or the patient's outpatient medical record may be of aid if the OBOT or OTP cannot be reached.
      ii. Confirm with the patient that they have been taking their home dose as prescribed. For patients taking buprenorphine, explain that if they have not been taking their buprenorphine as usual, or if they have been using other opioids, they may experience sudden withdrawal when they restart. Patients tend to disclose non-adherence when they understand the potential for precipitated withdrawal.
   e. Notify the outpatient buprenorphine or methadone provider of admission and anticipated length of stay so that hospitalized patients are not mistaken for program dropouts and continuity of care on discharge is smooth.
   f. If dose adjustments are made during hospitalization, inform the outpatient MAT provider.

6. **Hospitals are encouraged to establish MAT protocols and utilize a multidisciplinary team approach to initiate MAT for hospitalized patients with untreated OUD.**
   a. There are many well-developed resources to aid in building a MAT program within hospitals. Project SHOUT (Support for Hospital Opioid Use Treatment) is an excellent resource for clinicians and hospitals, with educational materials and protocols to facilitate adoption of MAT within hospitals.
   b. Several protocols from Project SHOUT are listed in the appendixes as references for hospitals developing MAT programs. More complete resources are available on the Project SHOUT website.
      i. Quick Guide: Buprenorphine Starts in the Hospital, Appendix VII
      ii. Quick Guide: Methadone Starts in the Hospital, Appendix VIII
      iii. Managing Acute Pain in Patients on MAT, Appendix XI
      iv. Effective MAT programs include all members of the hospitalist care team, including nurses and social workers. Hospitalist practices are encouraged to educate all team members in care and treatment of patients with OUD who are initiating or maintaining MAT. **TABLE 12** provides a checklist for starting a hospital MAT program.

(TABLE 12)

Checklist for Starting a Hospital MAT Program

- ☐ Identify program champions
- ☐ Engage key stakeholders, including hospital administration, pharmacy, nursing and social work
- ☐ Develop separate protocols for initiation of buprenorphine and methadone
- ☐ Ensure that patients admitted on medication for opioid use disorder (MOUD) are maintained on treatment
- ☐ Build order sets for inpatient prescribing
- ☐ Put MAT agents in hospital formulary
- ☐ Conduct provider education
- ☐ Develop patient education materials
- ☐ Establish protocols for discharge
- ☐ Establish ongoing quality assessment for hospital MOUD program

SOURCE: Project SHOUT[162]

7. Hospitalists are encouraged to provide hospitalized patients receiving MAT with adequate analgesia using ALTOs and, if needed, opioid agonists.

a. Opioid-sparing ALTO treatment modalities are recommended as first-line analgesia for all patients, including those on MAT. Appendix XI, Managing Acute Pain in Patients on MAT, provides further guidance.

b. The use of MAT agents will often alter the management of acute pain in the hospital setting.

c. Daily dosing of buprenorphine or methadone is generally inadequate for analgesia. The analgesic effects of both buprenorphine and methadone occur early in dosing and then wear off, so splitting doses provides some analgesia.[139,140] Splitting dosing of MAT opioid agonists to TID leverages the short-lived analgesia that follows dosing, though this change will not provide dramatically improved analgesia.

d. Clinicians are discouraged from reducing doses of buprenorphine or methadone prior to surgery, labor or in the setting of acute pain.[165,166] This applies to patients undergoing any painful procedure before, during and after the intervention. Continuing these medications improves pain control, reduces the use of opioid analgesics and reduces the risk of relapse after discharge.[165]

   i. Although it was previously believed that buprenorphine blocked the effects of full opioid agonists in the setting of acute pain, it is now known that the continuation of buprenorphine does not block the analgesic effect of opioids.[165]

   ii. Naloxone present in combination products (e.g., Suboxone) is not bioavailable and does not block analgesia. It is added solely as an abuse deterrent.

e. Patients and clinicians may not always be able to differentiate between withdrawal symptoms and discomfort from other causes. Completing the COWS scale with the patient to assess for symptoms of withdrawal may help distinguish withdrawal symptoms from symptoms due to other causes.

f. Anesthesia or pain service consultation may suggest specialized approaches to analgesia in the patient whose pain is not well-controlled.

Treatment of Opioid Use Disorders (OUD) continued

g. All patients may be counseled that treatment may not alleviate all pain and that manageable pain can be a useful guide to assessment and recovery.
h. Pain is a biopsychosocial phenomenon, and the importance of addressing the cognitive and affective components of pain cannot be understated. Consultation with social work, psychology or psychiatry may help a patient better manage pain during hospitalization. Cognitive and behavioral therapies may reduce pain and anxiety in some patients. Case management and psychosocial support is recommended for any patient with OUD.
i. Opioid analgesics may be offered to patients when ALTOs fail to control pain adequately. Patients receiving MAT with opioid agonists will have higher tolerance to opioids.
    i. Opioid-tolerant patients will likely require higher than typical doses of opioids.[105]
    ii. The prevalence of opioid-induced hyperalgesia (OIH) is unknown but likely complicates pain management for some opioid-dependent patients.
    iii. Avoid using mixed agonists/antagonists such as butorphanol and nalbuphine as they may cause precipitated withdrawal.

8. Naltrexone is a full opioid antagonist and its presence, particularly in long-acting formulations, may complicate management of pain with opioid agonists.

a. As a full opioid antagonist, naltrexone will block the analgesic effects of most opioids. Naltrexone comes in two forms, an oral tablet usually used for alcohol use disorders and a once per month, long-lasting depo injection used to treat OUD.
b. Patients who have previously been on naltrexone but are no longer taking the medication or have had it held or discontinued may have lower opioid tolerance than they did previously, so extreme caution is advised when prescribing opioids to these patients.
c. Hold naltrexone upon presentation for any acute pain that may require opioids.
d. For elective interventions where use of opioids is anticipated, hold oral naltrexone for 72 hours prior to the intervention[143,144] and hold IM naltrexone for at least 30 days, with PO dose bridging if necessary, until 72 hours prior to the intervention.
e. Pain management should maximize nonopioid interventions, including but not limited to NSAIDs, acetaminophen, ketamine, dexmedetomidine, local or regional anesthesia or conscious sedation with non-opioids as needed.
f. If necessary, high-dose opioids can be used to out-compete naltrexone at the opioid receptor. Patients should be closely monitored, at minimum with pulse-oximetry and telemetry, to ensure that over sedation and overdose do not occur.
g. After completion of opioid therapy, hold naltrexone for three to seven days from last opioid dose to avoid causing withdrawal symptoms.[143,144]

9. Hospitals are encouraged to establish relationships with MAT providers to provide "warm handoffs" for patients initiated on MAT in the hospital and ensure continuity of care after discharge.

a. OBOT programs can offer buprenorphine and naltrexone. They can be associated with addiction medicine practices or embedded in other primary care and subspecialty outpatient providers.
b. OTPs, sometimes referred to as "methadone clinics," are highly structured and regulated programs that administer methadone or buprenorphine daily on-site. For patients who benefit from more structure and added counseling support, OTPs offer a better option than OBOTs. Patients are initially administered either methadone or buprenorphine daily at the facility and have required psychosocial counseling. These facilities are heavily regulated by the DEA, the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Colorado Department of Human Services, Office of Behavioral Health.
c. In most urban areas, there exist multiple options for both OBOTs and OTPs. OpiRescue, a free mobile application and website, provides an up-to-date MAT treatment locator. It ranks providers based on the distance the patient lives from the provider and gives each provider's treatment options (methadone, buprenorphine or naltrexone). Additionally, SAMHSA provides a directory of MAT providers.

Treatment of Opioid Use Disorders (OUD) continued

d. Ideally, discharge planning for patients with OUD would begin upon hospitalization.
e. Hospitalist clinicians are encouraged to either directly distribute or prescribe naloxone to patients, families and caregivers of patients with OUD.
f. **APPENDIX X** provides a discharge checklist for hospitalists and social workers to aid in discharge planning.

10. All hospitalists are encouraged to consider obtaining X-waivers to prescribe buprenorphine for patients with OUD. This is especially critical in communities where outpatient MAT is difficult to access and may require further care coordination. Having an X-waiver allows hospitalists to better serve their patients and communities by prescribing buprenorphine to appropriate patients.

a. Under DATA 2000, physicians are required to have an X-waiver to prescribe and dispense buprenorphine for OUD. Any physician can order buprenorphine to be administered in the inpatient setting to treat opioid withdrawal.
b. X-waiver training is an eight-hour course for physicians and an additional 16 hours for nurse practitioners (NPs), physician assistants, clinical nurse specialists, certified registered nurse anesthetists and certified nurse-midwives. It provides valuable information to better understand OUD, MAT and special populations.
c. X-waivers can be completed online and through various organizations — below are several that offer this service.
    i. IT MATTTRs is based in Colorado and has provided training and financial incentives to clinicians to complete X-waiver training.
    ii. Providers' Clinical Support System for Medication Assisted Treatment (PCSS-MAT)
    iii. American Society of Addiction Medicine (ASAM)

Policy Recommendations

1. Local, state and federal funding for MAT services should be increased.

a. An adequate response to this public health crisis will require substantial investment in building a treatment system capable of serving the needs of all patients impacted by the opioid epidemic.

2. The X-waiver requirement for prescribing buprenorphine should be repealed.

a. It is not in the public interest to require a waiver for clinicians to treat patients with OUD, while no waiver is required to prescribe opioids.
b. While more than 900,000 physicians in the United States are licensed to write prescriptions for opioids, fewer than 32,000 are authorized to prescribe buprenorphine to treat addiction to opioids.[173]
c. The waiver requirement is a barrier to treatment and adds to the stigma around this disorder.
d. Similar deregulation in France allowed widespread usage of buprenorphine by all clinicians and has resulted in a 79% decline in opioid overdose deaths since deregulation in 1995.[174]
e. The Mainstreaming Addiction Treatment Act of 2019 (U.S. HR 2482) and any similar acts would eliminate the requirement for medical providers to obtain a waiver from the DEA to treat OUD with buprenorphine or any other Schedule III, IV or V drug. Such legislative action would significantly aid in closing the treatment gap and reducing overdose deaths.

Treatment of Opioid Use Disorders (OUD) continued

3. **Ease regulations around 42 CFR Part 2 to ease sharing of critical health data.**
   a. 42 CFR Part 2 requires a patient with SUD to explicitly give permission for an OTP or clinician treating a patient for SUD to share information, even with other clinicians caring for the patient.
   b. 42 CFR was created before HIPAA and provided an essential safeguard for privacy from 1975 until HIPAA was enacted in 1996. However, since HIPAA's enactment, 42 CFR Part 2 has created two separate and poorly communicating systems of care that too often place patients in danger.
   c. OTPs treating patients with methadone cannot disclose this fact to other health care professionals and, as a result, many PCPs, specialists or hospital-based physicians are left unaware of a patient's maintenance on methadone.
   d. This proves dangerous when physicians prescribe QT prolonging drugs, benzodiazepines or other medications that interact with methadone, resulting in potentially fatal drug interactions.
   e. The separation of SUD from the rest of medicine further stigmatizes a disease process that should be normalized and considered part of normal medical care.
   f. CO's CURE supports efforts to align 42 CFR Part 2 with HIPAA while ensuring that personal health information is not inappropriately shared with law enforcement, health insurers, data clearinghouses, employers or other entities outside the patient-physician relationship.
   g. CO's CURE joins the AMA, American Hospital Association, American Society of Addiction Medicine and others in their call to better align SUD treatment with the rest of medicine.

4. **Telemedicine for addiction treatment should be widely available, and telemedicine providers should be able to prescribe buprenorphine without a face-to-face encounter.**
   a. The 2018 Special Registration for Telemedicine Clarification Act (Title III, Chapter Four of PL 115-271) directs the DEA to amend its rules regarding the face-to-face encounter required by the 2008 Ryan Haight Act when prescribing controlled substances.
   b. The Ryan Haight Act is an unnecessary barrier to treating patients with OUD via telehealth in rural areas.
   c. The DEA is expected to soon release new rules that will allow the prescribing of buprenorphine via telemedicine without an initial face-to-face encounter.
   d. CO's CURE encourages a loosening of the Ryan Haight Act's restrictions to allow clinicians to better treat patients with OUD in rural and other hard-to-access areas.

5. **Decrease regulations surrounding OTPs to reduce barriers for methadone maintenance treatment.**
   a. To be enrolled in an OTP and receive treatment with methadone, a patient must have been using opioids for at least 12 months. No patient should be required to wait 12 months for treatment for a life-threatening disease.
   b. Counseling requirements within OTPs should be decreased. While most patients benefit from case management and counseling, the medical ethic of patient autonomy is violated by the rigid requirements mandated by state and federal regulations.
   c. A patient's ability to access proven medications like methadone and buprenorphine should not be conditional upon other treatment modalities. There are many other disease states that would benefit from psychosocial therapy in addition to medication management, but one should not be a requirement for the other.
   d. Allow NPs to have a full scope practice within OTPs. Current regulations prohibit NPs from ordering methadone within an OTP. No such restrictions on NPs exist in other health care settings.

6. **Subsidies should be provided for OTPs in rural areas.**
   a. OTPs are currently clustered around Colorado's Front Range. There are only two on the Western Slope and none on the Eastern Plains.
   b. Not all patients respond to buprenorphine, and methadone may be the only effective treatment for a significant number of patients with OUD.
   c. Some patients significantly benefit from the structure of an OTP.
   d. OTPs are not financially viable in rural areas because there are too few patients to cover operational expenses.
   e. Incentives provided to support the development of new OTPs in rural areas of the state would help patients who live in these currently underserved communities.

The Future and Ending the Opioid Epidemic in Colorado

As clinicians, we stand with our patients and their families who are impacted by opioid use disorder. We have witnessed the devastation this epidemic has wrought across Colorado and are committed to ending the suffering of our patients and communities.

The CO's CURE guidelines offer a vision for how clinicians and health care leaders on the front lines of this epidemic can change how we deliver care to better serve our patients. If we take to heart the need to reduce our opioid usage, we can decrease the number of Coloradans who develop opioid use disorders in our care. If we embrace and continue to innovate alternatives to opioids for pain control, we will be able to manage pain more effectively and safely than ever before. If we integrate harm reduction into our practices and strive to better understand patients who struggle with injection drug use and OUD, we can end the stigma that surrounds this disease and decrease overdose deaths. If we consistently offer medication-assisted treatment to every patient with OUD for whom we care, we can close the treatment gap and ensure that all who yearn for recovery are provided the tools and the resources they need. The time to make these changes is now. In doing so, we can uphold our sacred oath to serve our patients and communities in their times of need and resolve to address this epidemic together.

CO's CURE aims to harness the power of health care professionals across Colorado working together with common purpose. CO's CURE resources are available to any Colorado physician. As you endeavor to change your practice and adopt these guidelines, you can rest assured that medical practices and specialties across our state are doing the same. CO's CURE represents a philosophy of care that is inclusive and collaborative and recognizes that the only way we can end the epidemic in Colorado and across the nation is by acting together.

On behalf of our sponsoring organizations, Colorado Hospital Association, Colorado Medical Society and Colorado Consortium for Prescription Drug Abuse Prevention, as well as the 13 medical specialties that have stepped forward to participate, we offer our gratitude and appreciation for the care and consideration you give these guidelines. The health of our state and its people depends on clinicians and leaders like you who are willing to be agents of change. Together, we can make a profound difference in the lives of Coloradans as we implement new, better standards of care. Together we can bring this deadly epidemic to an end.

Debra Parsons, MD, FACP
PRESIDENT, COLORADO MEDICAL SOCIETY

Darlene Tad-y, MD, SFHM
VICE PRESIDENT CLINICAL AFFAIRS, COLORADO HOSPITAL ASSOCIATION

Donald E. Stader III, MD, FACEP
PAIN MANAGEMENT AND OPIOID POLICY PHYSICIAN ADVISOR, COLORADO HOSPITAL ASSOCIATION

Robert Valuck, PhD, RPh, FNAP
EXECUTIVE DIRECTOR, COLORADO CONSORTIUM FOR PRESCRIPTION DRUG ABUSE PREVENTION

Appendices

I. Resources for Patients
II. Materials Used for IV Drug Use
III. Steps to Injecting Heroin and Unsafe Practices
IV. Map and Listing of Syringe Access Programs in Colorado (updated March 2020)
V. Rapid Opioid Dependence Screen
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VII. Quick Guide: Buprenorphine Starts in the Hospital
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X. Discharge Checklist for Patients Receiving MAT
XI. Managing Acute Pain in Patients on MAT
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Appendix I

Resources for Patients

PRESCRIPTION OPIOIDS: WHAT YOU NEED TO KNOW

Prescription opioids can be used to help relieve moderate-to-severe pain and are often prescribed following a surgery or injury, or for certain health conditions. These medications can be an important part of treatment but also come with serious risks. It is important to work with your health care provider to make sure you are getting the safest, most effective care.

WHAT ARE THE RISKS AND SIDE EFFECTS OF OPIOID USE?

Prescription opioids carry serious risks of addiction and overdose, especially with prolonged use. An opioid overdose, often marked by slowed breathing, can cause sudden death. The use of prescription opioids can have a number of side effects as well, even when taken as directed:

- Tolerance—meaning you might need to take more of a medication for the same pain relief
- Physical dependence—meaning you have symptoms of withdrawal when a medication is stopped
- Increased sensitivity to pain
- Constipation
- Nausea, vomiting, and dry mouth
- Sleepiness and dizziness
- Confusion
- Depression
- Low levels of testosterone that can result in lower sex drive, energy, and strength
- Itching and sweating

receiving prescription opioids long term in a primary care setting struggles with addiction.

* Findings from one study

RISKS ARE GREATER WITH:

- History of drug misuse, substance use disorder, or overdose
- Mental health conditions (such as depression or anxiety)
- Sleep apnea
- Older age (65 years or older)
- Pregnancy

Avoid alcohol while taking prescription opioids. Also, unless specifically advised by your health care provider, medications to avoid include:

- Benzodiazepines (such as Xanax or Valium)
- Muscle relaxants (such as Soma or Flexeril)
- Hypnotics (such as Ambien or Lunesta)
- Other prescription opioids

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

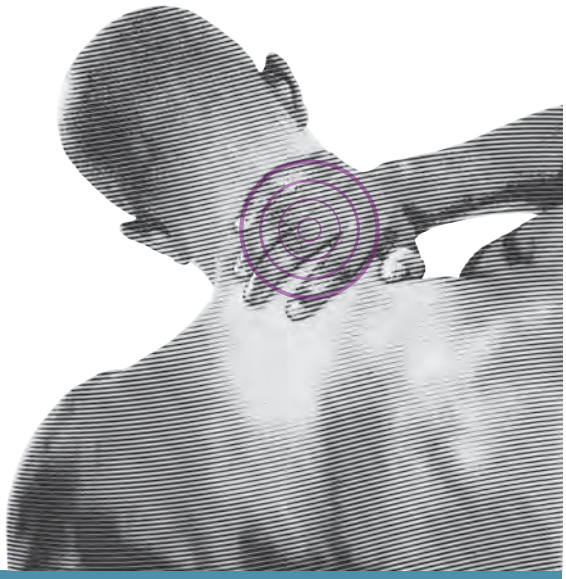
American Hospital Association®

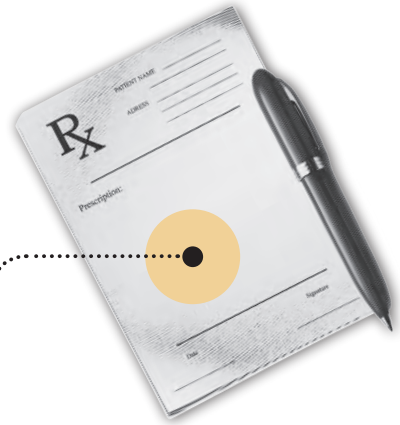
CS264107C May 9, 2016

KNOW YOUR OPTIONS

Talk to your health care provider about ways to manage your pain that don't involve prescription opioids. Some of these options **may actually work better** and have fewer risks and side effects. Options may include:

- Pain relievers such as acetaminophen, ibuprofen, and naproxen
- Some medications that are also used for depression or seizures
- Physical therapy and exercise
- Cognitive behavioral therapy, a psychological, goal-directed approach, in which patients learn how to modify physical, behavioral, and emotional triggers of pain and stress.





Be Informed!

Make sure you know the name of your medication, how much and how often to take it, and its potential risks & side effects.

IF YOU ARE PRESCRIBED OPIOIDS FOR PAIN:

- Never take opioids in greater amounts or more often than prescribed.
- Follow up with your primary health care provider within ___ days.
  - Work together to create a plan on how to manage your pain.
  - Talk about ways to help manage your pain that don't involve prescription opioids.
  - Talk about any and all concerns and side effects.
- Help prevent misuse and abuse.
  - Never sell or share prescription opioids.
  - Never use another person's prescription opioids.
- Store prescription opioids in a secure place and out of reach of others (this may include visitors, children, friends, and family).
- Safely dispose of unused prescription opioids: Find your community drug take-back program or your pharmacy mail-back program, or flush them down the toilet, following guidance from the Food and Drug Administration (www.fda.gov/Drugs/ResourcesForYou).
- Visit www.cdc.gov/drugoverdose to learn about the risks of opioid abuse and overdose.
- If you believe you may be struggling with addiction, tell your health care provider and ask for guidance or call SAMHSA's National Helpline at 1-800-662-HELP.

LEARN MORE | www.cdc.gov/drugoverdose/prescribing/guideline.html

SURGICAL

YOU are the most important member of your healthcare team. Ask questions and get the FACTS before taking opioids to manage your pain.

WHAT IS AN OPIOID?

An opioid is a strong prescription pain medication. Possible side effects include nausea, vomiting, sleepiness, dizziness and/or constipation.

Common opioids include:

Generic Name	Brand Name
Codeine	Tylenol® #3* or #4*
Fentanyl	Duragesic®
Hydrocodone	Vicodin®*, Norco®*
Hydromorphone	Dilaudid®
Methadone	Methadose®
Morphine	MS Contin®, Kadian
Oxycodone	Percocet®*, OxyContin®
Oxymorphone	Opana®
Tramadol	Ultram®, Ultracet®*

* Contains acetaminophen (Tylenol). Use caution if you're also taking acetaminophen separately.

SAFE STORAGE AND DISPOSAL

Store opioids out of sight and reach of children, teens, and pets

- Store opioids in private areas and lock up your pills if possible.
- Do not store your opioids in common rooms in the house (like bathrooms, kitchens) or in purses.
- Keep a count of how many pills you have left.

Dispose of all unused opioids

- Use a permanent medication drop box. To find one near you, visit: **Michigan-OPEN.org/takebackmap**.
- Drop off at a community Medication Take Back event.
- Use your household trash as a last resort.
  - Mix opioids (do not crush) with used coffee grounds or kitty litter in a plastic bag and throw away.
  - Scratch out personal information on the prescription label and dispose of the original container.

Do NOT flush opioids down the toilet.

Michigan-OPEN.org

Michigan OPEN is partially funded by the Michigan Department of Health and Human Services.

LEARN THE FACTS:

opioids & pain management

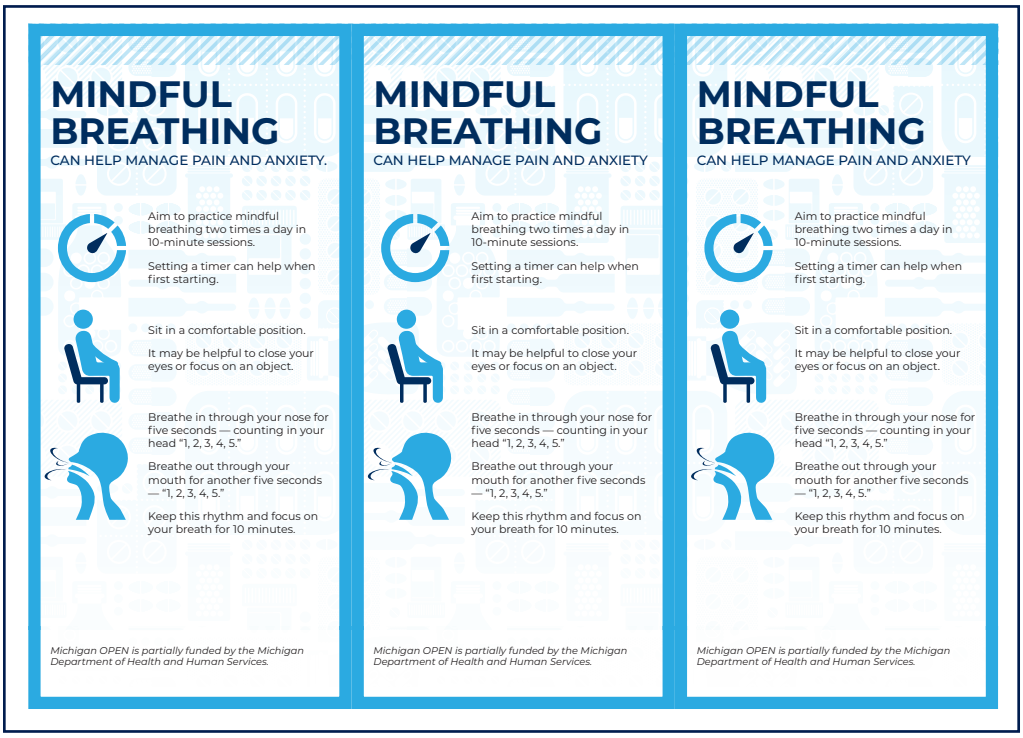
OPEN
OPIOID PRESCRIBING ENGAGEMENT NETWORK

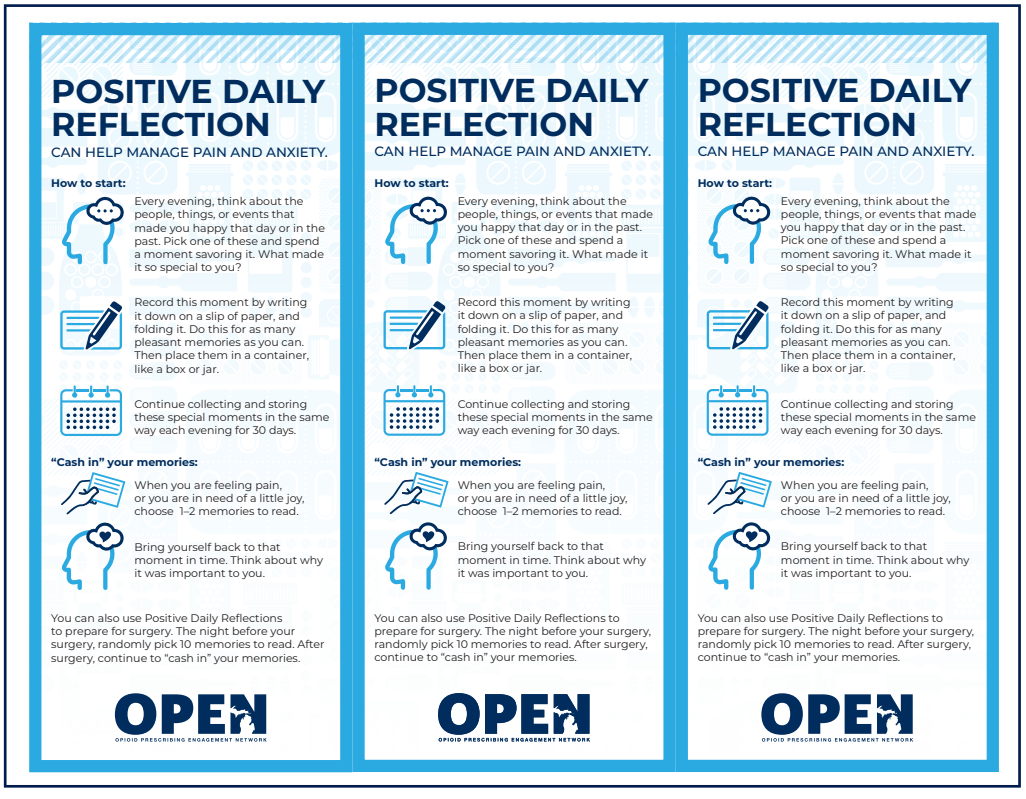
Appendix I continued

Used with permission from www.michigan-open.org

Appendix I continued

Patient Instructions for Managing Surgical Pain Without Opioids





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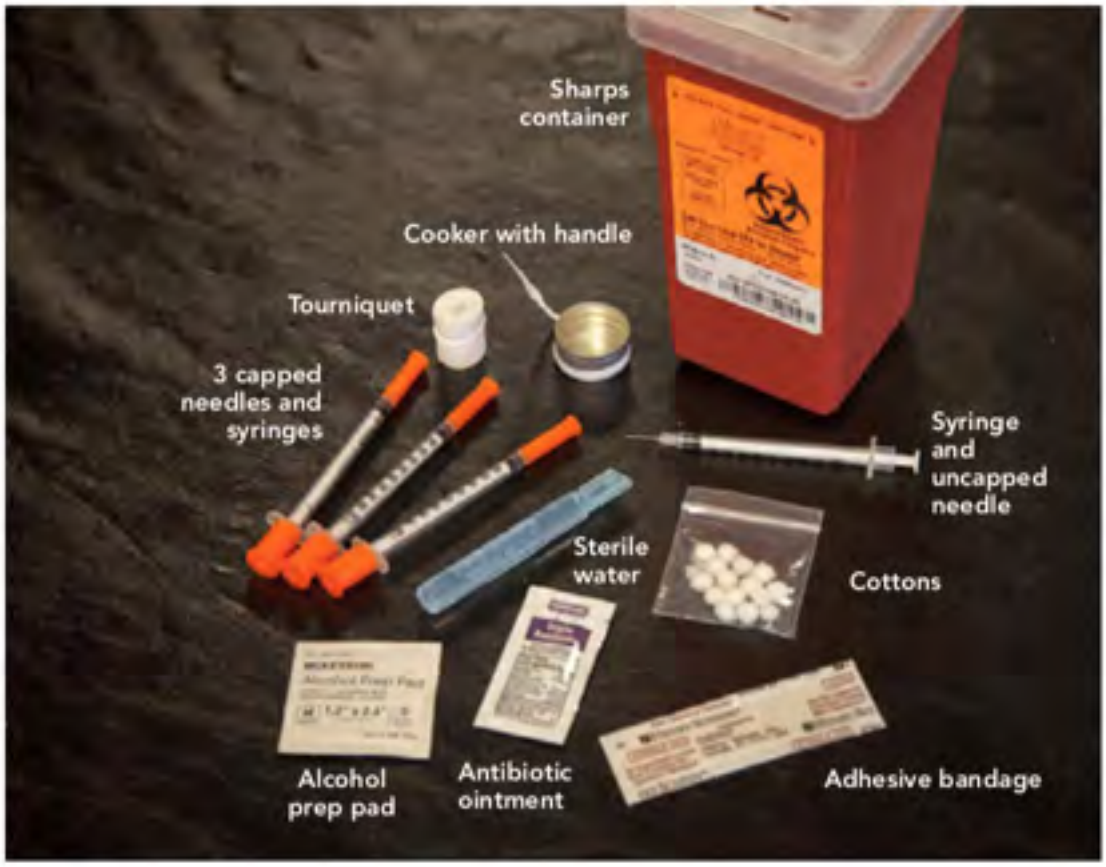
Appendix II

Materials Used for IV Drug Use



SOURCE: 2017 Colorado ACEP Opioid Prescribing & Treatment Guidelines

Appendix III

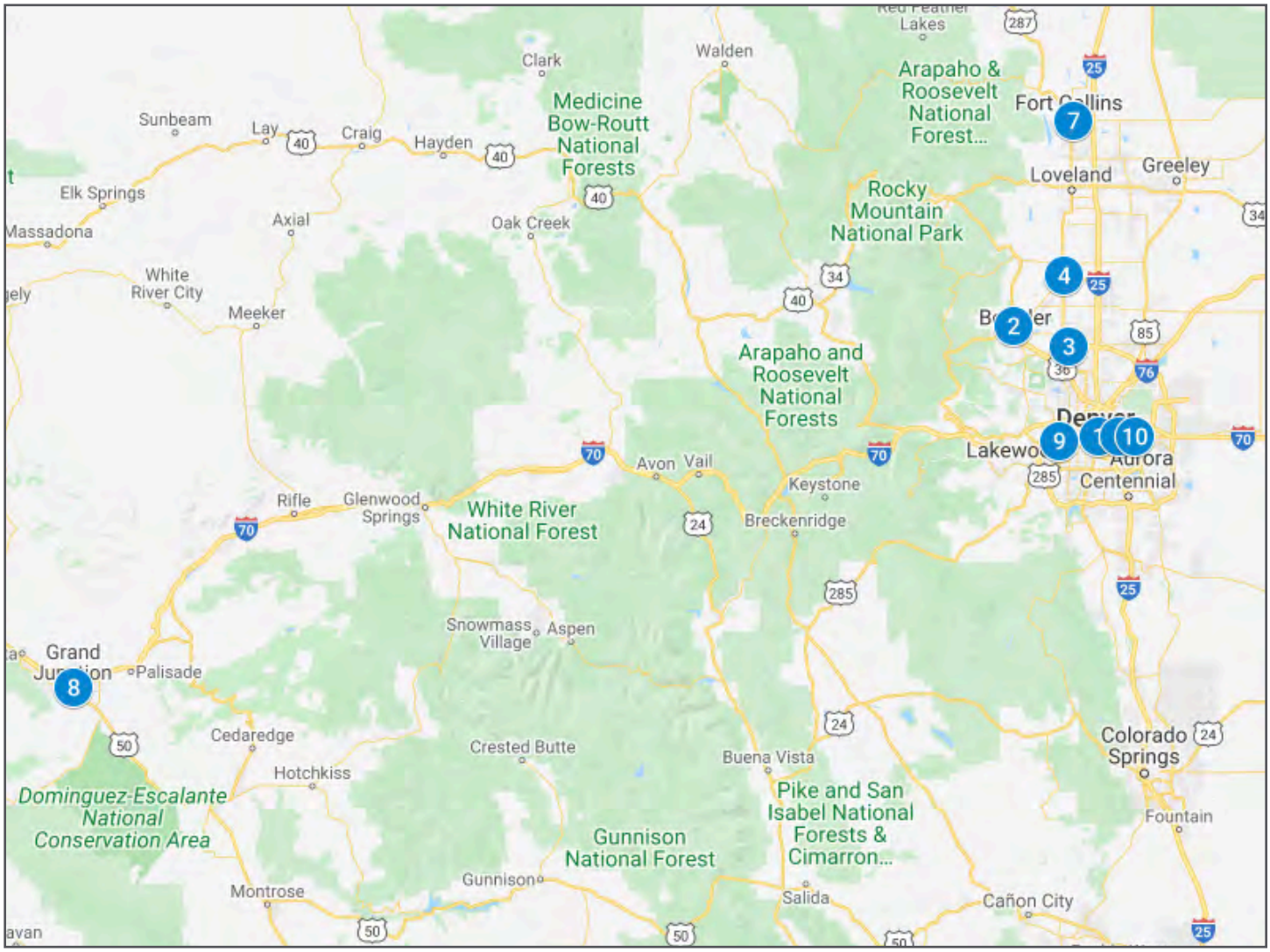
Steps to Injecting Heroin and Unsafe Practices

Steps to Injection Heroin	Unsafe Practices Associated with Injection Complications
1. Heroin (especially black tar heroin) must be dissolved into an injectable solution. a. Heroin is placed in a cooker or spoon. b. Water is added to the cooker. c. Water is either mixed or heated to help dissolve the heroin. d. Some heroin comes in a base form that is dissolved using citric acid or another acidic solution. This is more common with European heroin. 2. Dissolved heroin is filtered into a syringe. a. A filter (most often a small cotton ball) is used to draw the drug into a syringe and remove particulate matter. b. A needle attached to a syringe is placed near or into the cotton, and heroin is drawn into the syringe. 3. An injection site is identified. A tourniquet is often used to help keep veins engorged to ease injection. 4. The needle is injected into the patient's vein, and a syringe plunger is compressed to deliver the drug. 5. The needle is removed, and the tourniquet is released.	1. Sharing equipment or borrowing equipment from other PWID. 2. Reusing equipment, including spoons, cottons, cookers (if reused, equipment should be cleaned and sanitized). 3. Using unsanitary water or saliva to dissolve heroin. 4. Using bottled water that has been used or contaminated by saliva. 5. Licking a needle prior to injection. 6. Failing to clean hands or skin prior to injecting. 7. Injecting into unsafe veins in the neck or groin. 8. "Skin popping" (subcutaneous injection) or "muscling" (intramuscular injection). 9. Dissolving heroin with an unsafe acidic solution, such as lime or orange juice. 10. Not having access to naloxone or being unaware of how to prevent an overdose.

Appendix IV

Map and Listing of Syringe Access Programs in Colorado

(updated March 2020)



Appendix IV

Syringe Access Programs in Colorado

	Name	Address	Hours	Phone
1	Harm Reduction Action Center	112 E. 8th Avenue Denver, CO 80203	Mon–Fri 9 a.m.–12 p.m.	303.572.7800
2	The Works	3450 Broadway Boulder, CO 80304	Mon–Fri 10:30 a.m.–4:30 p.m.	303.413.7533 303.441.1100
3	Boulder County Public Health	1735 S. Public Road Lafayette, CO 80026	Tues & Thurs 10:30 a.m.–4:30 p.m.	720.564.2706
4	Boulder County Public Health	515 Coffman Street, #200 Longmont, CO 80501	Mon–Fri 10:30 a.m.–4:30 p.m.	303.678.6166
5	Southern Colorado AIDS Project	807 N. Greenwood Street Suite 200 Pueblo, CO 81003	Mon–Fri 10 a.m.–12 p.m. & 1:30–4 p.m.	719.621.1105
6	Denver Colorado AIDS Project	6260 E. Colfax Avenue Denver, CO 80220	Mon–Thurs, 1–6 p.m. Fri, 12–5 p.m.	303.837.0166
7	North Colorado AIDS Project	400 Remington Street, #100 Fort Collins, CO 80524	Mon, Thurs & Fri 1–5:45 pm Tues, 2–5:45 p.m. Wed, 1–6:45 p.m.	970.484.4469
8	West Colorado AIDS Project	805 Main Street Grand Junction, CO 81501	Mon, Wed & Fri 12–4:45 p.m.	970.243.2437
9	Points West Syringe Service Program	645 Parfet Street Lakewood, CO 80215	Mon & Thurs 8 a.m.–6 p.m. Wed & Fri 8 a.m.–5 p.m.	303.239.7078
10	Aurora Syringe Access Services	1475 Lima Street Aurora, CO 80010	Mon–Thurs 1–4 p.m.	303.363.3077
11	Southern Colorado Harm Reduction Association	1249 E. Routt Avenue Pueblo, CO 81004	Sat 12:30–4:30 p.m.	719.289.7149
12	Rocky Mountain Cares LifePoint	Mobile SAP for DenverArea	Mon, Wed & Fri Mobile Outreach Exchange; hours vary	720.385.6898

Appendix V

Rapid Opioid Dependence Screen (RODS)

Instructions: [Interviewer reads] The following questions are about your prior use of drugs. For each question, please indicate "yes" or "no" as it applies to your drug use during the last 12 months.

1. Have you ever taken any of the following drugs?
   a. Heroin ☐ Yes ☐ No
   b. Methadone ☐ Yes ☐ No
   c. Buprenorphine ☐ Yes ☐ No
   d. Morphine ☐ Yes ☐ No
   e. MS Contin ☐ Yes ☐ No
   f. Oxycontin ☐ Yes ☐ No
   g. Oxycodone ☐ Yes ☐ No
   h. Other opioid analgesics ☐ Yes ☐ No
      (e.g., Vicodin, Darvocet, etc.)

If any drug in question 1 is coded "yes," proceed to quesitons 2 to 8.

If all drugs in question 1 are "no," skip to end and code "no" for opioid dependent.

2. Did you ever need to use more opioids to get the same high as when you first started using opioids? ☐ Yes ☐ No
3. Did the idea of missing a fix (or dose) ever make you anxious or worried? ☐ Yes ☐ No
4. In the morning, did you ever use opioids to keep from feeling "dope sick" or did you ever feel "dope sick?" ☐ Yes ☐ No
5. Did you worry about your use of opioids? ☐ Yes ☐ No
6. Did you find it difficult to stop or not use opioids? ☐ Yes ☐ No
7. Did you ever need to spend a lot of time/energy on finding opioids or recovering from feeling high? ☐ Yes ☐ No
8. Did you ever miss important things like doctor's appointments, family/friend activities, or other things because of opioids? ☐ Yes ☐ No

Scoring Instructions: Add number of "yes" responses for questions 2 to 8. If total is > 3, code "yes" for opioid dependent. If total is < 2, code "no" for opioid dependent.

Opioid Dependent: ☐ Yes ☐ No

Appendix VI

Clinical Opioid Withdrawal Scale (COWS)

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient's Name_____ Date and time _____

Reason for this assessment_____

Resting pulse rate: _____ beats/minute *(measured after patient has been sitting or lying down for 1 minute)*
0 pulse rate ≤80
1 pulse rate 81-100
2 pulse rate 101-120
4 pulse rate >120

GI upset *(in the last 30 minutes)*
0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhea
5 multiple episodes of diarrhea or vomiting

Sweating *(in last 30 minutes, and not accounted for by room temperature or patent activity)*
0 no report of chills or flushing
1 subjective report of chills or flushing
2 flushed or observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face

Tremor *(observation of outstretched hands)*
0 no tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching

Restlessness *(observed during assessment)*
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 unable to sit still for more than a few seconds

Yawning *(observation during assessment)*
0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment
4 yawning several times/minute

Pupil size
0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
2 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Anxiety or irritability
0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable or anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Bone or joint aches *(if patient was having pain previously, only the additional component attributed to opioid withdrawal is scored)*
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

Gooseflesh skin
0 skin is smooth
3 piloerection of skin can be felt or hairs standing up on arms
5 prominent piloerection

Runny nose or tearing: *not accounted for by cold symptoms or allergies)*
0 not present
1 nasal stuffiness or unusually moist eyes
2 nose running or tearing
4 nose constantly running or tears streaming down cheeks

TOTAL SCORE:_____

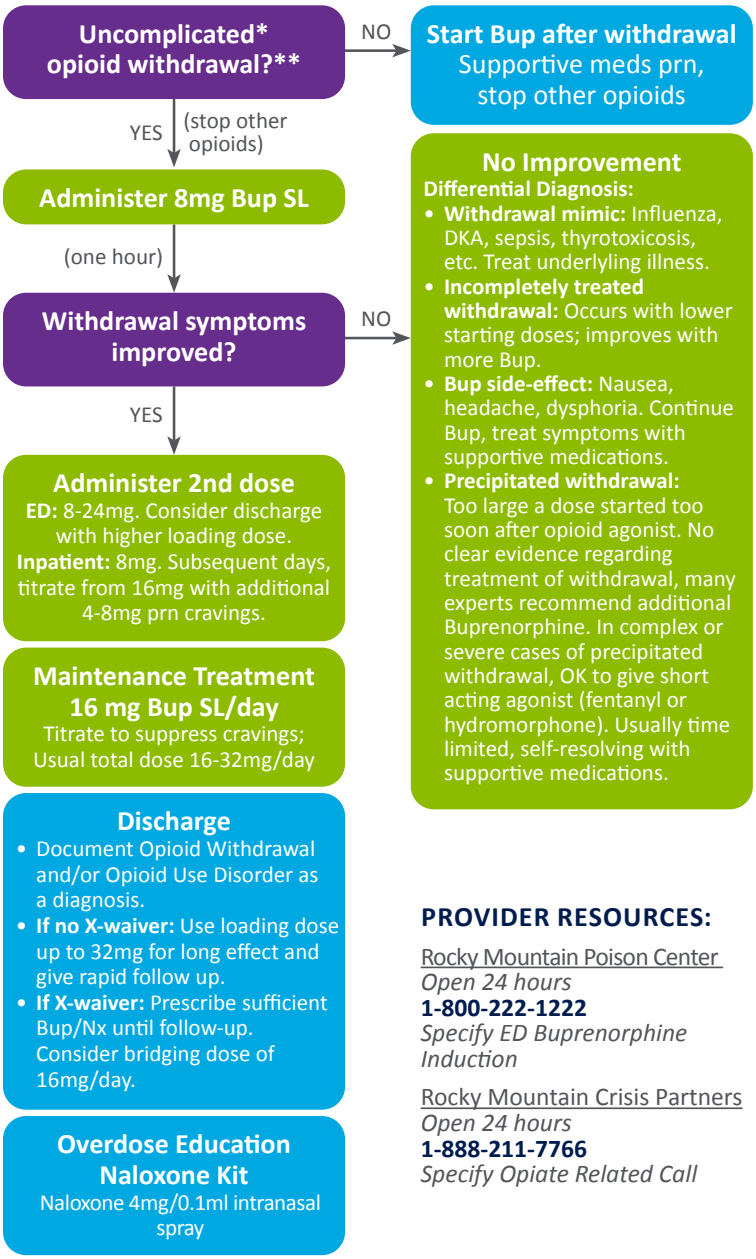
The total score is the sum of all 11 items.

Initials of person completing assessment_____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawl

Appendix VII

Quick Guide: Buprenorphine Starts in the Hospital



PROVIDER RESOURCES:

Rocky Mountain Poison Center
Open 24 hours
1-800-222-1222
Specify ED Buprenorphine Induction

Rocky Mountain Crisis Partners
Open 24 hours
1-888-211-7766
Specify Opiate Related Call

Buprenorphine Dosing

- Either Bup or Bup/Nx (buprenorphine/naloxone) films or tab sublingual (SL) are OK.
- If unable to take oral/SL, try Bup 0.3mg IV/IM.
- OK to start with lower initial dose: Bup 2-4mg SL.
- Total initial daily dose above 16mg may increase duration of action beyond 24 hrs.
- Bup SL onset 15 min, peak 1 hr, steady state 7 days.
- May dose qday or if co-exisiting chronic pain split dosing TID/QID.

*Complicating Factors

- Altered mental status, delirium, intoxication
- Severe acute pain, trauma or planned large surgeries
- Organ failure or other severe medical illness

Recent methadone use

**Diagnosing Opioid Withdrawal
Subjective symptoms AND one objective sign

Subjective: Patient reports feeling "bad" due to withdrawal (nausea, stomach cramps, body aches, restlessness, hot and cold, stuffy nose)
Objective: [at least one] restlessness, sweating, rhinorrhea, dilated pupils, watery eyes, tachycardia, yawning, goose bumps, vomiting, diarrhea, tremor
Typical withdrawal onset:
≥ 12 hrs after short acting opioid
≥ 24 hrs after long acting opioid
≥ 48 hrs after methadone (can be >72 hrs)
If unsure, use COWS (clinical opioid withdrawal scale). Start if COWS ≥ 8 AND one objective sign.
If Completed Withdrawal: Typically >72 hrs since last short-acting opioid, may be longer for methadone. Start Bup 4mg q4h prn cravings, usual dose 16-32mg/day. Subsequent days, OK to decrease frequency to qday

Opioid Analgesics

- Pause opioid pain relievers when starting Bup.
- OK to introduce opioid pain relievers after Bup is started for breakthrough pain. Do not use methadone with Bup.

Supportive Medications

- Can be used as needed while waiting for withdrawal or during induction process.

Pregnancy

- Bup monoproduct or Bup/Nx OK in pregnancy.
- Consider referencing buprenorphine in pregnancy guide.

Appendix VIII

Quick Guide: Methadone Starts in the Hospital

Day 1: max daily dose 40 mg methadone

First dose
- Check COWS and Ramsay
- Administer 10-30mg methadone
- Recheck Ramsay in 1 hour

After 4 hours
- If endorsing withdrawal/cravings, check Ramsay
- If no sedation, order additional 5 - 10 mg dose
- Recheck Ramsay in 1 hour

After 4 hours
- If endorsing withdrawal/cravings, check Ramsay
- If no sedation and not at max daily dose, order additional 5-10 mg dose
- Recheck Ramsay in 1 hour

Day 2: max daily dose 50 mg methadone

First dose
- Check Ramsay, proceed if no sedation
- Give total daily dose from day 1 as single dose
- Recheck Ramsay in 1 hour

After 4 hours
- If endorsing withdrawal/cravings, check Ramsay
- If no sedation, order additional 5 - 10 mg dose
- Recheck Ramsay in 1 hour

After 4 hours
- If endorsing withdrawal/cravings, check Ramsay
- If no sedation and not at max daily dose, order additional 5-10 mg dose
- Recheck Ramsay in 1 hour

Ramsay sedation score:

1. Anxious/restless
2. Cooperative/oriented/tranquil
3. Response to commands
4. Brisk response to stimulus
5. Sluggish response to stimulus
6. No response to stimulus

Testing prior to first dose:

- ☐ Urine toxicology
- ☐ EKG for QTc interval
- ☐ Urine pregnancy test (PRN childbearing potential)
- ☐ DSM 5 criteria for opioid use disorder
- ☐ CURES report
- ☐ Consider HIV, HepB, HepC testing
- ☐ ***Pregnancy:***
  non-stress test or fetal heart tones as indicated

Contraindications/cautions:

Call experts as needed, may still start with support

- Allergy to methadone
- Respiratory depression
- Ramsay sedation scale ≥ 4
- QTC > 500
- Recent use of benzodiazepines, alcohol, or other sedatives
- Severe liver disease
- Comorbid alcohol withdrawal

Initial dose selection:

Anywhere from 10-30 mg may be selected. Patients should be dosed according to tolerance (expect lower tolerance with non-daily users, oral hydrocodone, smoked opium users, etc). May use morphine equivalent calculator as a guide. Withdrawal severity is not well correlated with tolerance.

Discharge prescriptions:

- Methadone may not be prescribed for opioid use disorder. Must be administered in methadone clinic.
- Naloxone 4 mg/0.1 ml intranasal PRN opioid overdose. Spray 0.1 ml into one nostril, call 911, if no response in 2-3 minutes repeat with second device in additional nostril. #1 pack of 2, 3 refills
- Consider pre-exposure HIV prophylaxis

Day 3: Follow instruction for day 2 above, but with first dose being total daily dose from day 2. Max dose on day 3 is 60 mg.
Subsequent days: Do not increase dose for 5 days. Can increase by 10 mg every 5 days subsequently.

Somnolence/respiratory depression: All patients should have order for naloxone 0.1 mg IV/IM q 1 to 2 minutes PRN RR < 8/min and difficult to arouse or Ramsay sedation scale ≥ 5, x 3 doses. Caution: the use of additional opioids or benzodiazepines during this time can increase risk of somnolence/respiratory depression, and should be avoided if possible. If RR < 8 or Ramsay > 2 at any time, do not give additional methadone. Consider dose decrease, and consult with experts.

Adjunctive meds: The following can be prescribed prn for symptoms of withdrawal (check for contraindications and drug-drug interactions).

- Acetaminophen 650 mg PO q 6 hours daily PRN pain
- Clonidine 0.1-0.3 mg PO q 6-8 hours PRN w/d symptoms (NTE 1.2 mg/day, hold if BP < 100/70)
- Diphenhydramine 25-50 mg, PO q 8 hours PRN insomnia/anxiety
- Loperamide 4 mg PO initially, then 2 mg PRN each additional loose stool (NTE 16 mg/24 hours)
- Ondansetron 4 mg PO q 6 hours PRN nausea
- Trazodone 50 mg PO qhs PRN insomnia
- Melatonin 3 mg PO qhs PRN insomnia

For clinical questions:

UCSF Substance Use Warm-line 855-300-3595 or https://tinyurl.com/yd4ymyx6 (M-F 9am-8pm ET)

SHOUT
SUPPORT FOR HOSPITAL OPIOID USE TREATMENT

SOURCE: Project SHOUT

Appendix IX

Adjuvant Treatment of Opioid Withdrawal

The treatments of choice for acute opioid withdrawal are buprenorphine or methadone. In the rare cases where these medications are clinically contraindicated, where a patient refuses treatment with an opioid agonist or where a patient has been using methadone illicitly but has no access to an OTP after discharge, hospitalists are encouraged to employ the use of alpha-2-agonists, antihistamines, anticholinergics, antiemetics and NSAIDs to ameliorate withdrawal symptoms. While generally not life-threatening, opioid withdrawal causes significant discomfort and dysphoria. Supportive and symptomatic treatment with the following non-narcotic agents also is encouraged as an adjunct to initiating opioid agonist therapy:

ALPHA-2-AGONISTS

a. Clonidine is effective for ameliorating withdrawal symptoms.[173] Typical regimens consist of 0.1–0.3 mg given orally in two to four doses/day (up to a maximum of 1.2 mg/day) for seven to 10 days. Compared to placebo, the drug is associated with a greater incidence of adverse effects, including hypotension, lethargy, drowsiness and dry mouth (most commonly seen in the first few days of treatment).
b. Transdermal systems deliver doses that are equivalent to oral formulations, but in an easy-to-use weekly patch. For example, the Catapres-TTS-1 patch delivers a dose that is equivalent to an oral dose of 0.1 mg twice daily for seven days; however, adverse effects are unpredictable due to the lack of titration.
c. Lofexidine is an alpha-2-agonist approved by the FDA in 2018 for the treatment of opioid withdrawal. While lofexidine and clonidine have been shown to be equally effective in the treatment of opioid withdrawal, lofexidine produces less hypotension.[173] Lofexidine, however, is significantly more expensive than clonidine.

Antiemetics

Agents such as ondansetron, promethazine and prochlorperazine are very familiar to hospitalists and can be used for nausea and vomiting associated with withdrawal.

a. ANTICHOLINERGICS: Medications such as dicyclomine may be given to alleviate abdominal cramping and pain.
b. ANTIHISTAMINES: Hydroxyzine can be used for anxiety and dysphoria.
c. NSAIDs: Ibuprofen, naproxen and ketorolac can be used for headache, myalgias and pain.
d. BENZODIAZEPINES (CAUTION): These agents generally are not recommended, as their potential for abuse and side effects typically outweighs the benefits; patients must be strictly monitored.

Appendix X

Discharge Checklist for Patients Receiving MAT

For patients who were on MAT at time of admission:

- ☐ Coordinate with patient's buprenorphine provider or methadone clinic so that there is not a gap in care.
  a. If patient's home dose was decreased or split during hospitalization, dose is recommended to be returned to home dosing prior to discharge, if safe to do so. Provider may contact consult services or patient's clinic provider to discuss retitration.
  b. For methadone, call the methadone clinic on admission and one to two days prior to discharge to ensure that the patient is able to return to the clinic after discharge.

For patients initiated on buprenorphine during hospital stay:

- ☐ Social worker or clinicians are encouraged to call local buprenorphine prescriber to arrange a "warm handoff" and appointment for patient after discharge. Ideally, this appointment will be within three days of discharge.
- ☐ Ensure that the patient has enough buprenorphine or buprenorphine/naloxone at home to last until their next visit with their prescriber.
- ☐ Hospital providers with DEA waivers to prescribe buprenorphine can write a discharge prescription for buprenorphine or buprenorphine/naloxone to last until the patient's next appointment.
- ☐ If no X-waiver licensed provider is available, one of the following would ideally occur:
  a. Appointment with X-waivered provider the day after discharge.
  b. Return to the ED for administration of buprenorphine. This is legal for up to three days as a bridge to the first outpatient appointment.[139]
  c. Consider a loading dose on the day of discharge of up to 32 mg — this may prevent withdrawal for up to 72 hours, without clinically significant sedation or respiratory depression.
- ☐ Skilled nursing facilities (SNF) that are not classified as hospitals can only keep patients on buprenorphine if they have an outside provider. Discuss these details with the SNF early in the process.
- ☐ Dispense or prescribe naloxone.

For patients initiated on methadone during hospital stay:

- ☐ Social worker or clinician is encouraged to call local OTP to arrange a "warm handoff" and availability for intake after discharge. Ideally, this appointment will be the day of or day after discharge.
- ☐ Some OTPs require that a patient discharged on a weekend or holiday be transported to the clinic on a non-holiday weekday to complete the intake process prior to hospital discharge.
- ☐ You cannot prescribe methadone on discharge for treatment of OUD. The patient will need to go to the designated OTP, usually early the day after discharge. The OTP will often request a faxed discharge summary prior to the patient's arrival.
- ☐ SNFs that are not classified as hospitals can only keep patients on methadone if patients are already enrolled in an outpatient methadone program — discuss these details with the SNF early in the process.
- ☐ Dispense or prescribe naloxone.

SOURCE: Adapted from Project Shout

Appendix XI

Managing Acute Pain in Patients on MAT

Managing Acute Pain in Patients on Medication for Addiction Treatment (MAT):

- The use of methadone, buprenorphine or naltrexone for the treatment of OUD may complicate acute pain management.
- Analgesia should be offered to patients receiving MAT who are in pain. A patient's usual dose of buprenorphine or methadone is generally inadequate to provide adequate pain control.
  - Splitting home doses of buprenorphine or methadone three times per day leverages the early analgesic effects of these medications; however, the analgesic effect is inadequate to address moderate or severe pain.
- The use of pharmacologic and procedural alternatives to opioids should be maximized in patients receiving MAT.
- Consider consulting anesthesia or pain medicine for the use of neuraxial or regional anesthetic techniques in patients with difficult-to-manage acute pain that may benefit from these procedures.
- The following agents may be of particular value for the treatment of patients receiving MAT.
  - Any patient in pain should receive scheduled APAP and an NSAID, except when clinically contraindicated.
  - Gabapentinoids: Gabapentin (300–600 mg PO three times per day) OR pregabalin (75–150 mg PO twice daily) can reduce pain and opioid consumption in hospitalized patients; careful monitoring for oversedation and respiratory depression is required.
  - Alpha-2 agonists: Clonidine is anxiolytic and analgesic with significant opioid-sparing effects (e.g., clonidine 0.1–0.3 mg PO every six to eight hours as needed for pain or anxiety [NTE 1.2 mg/day, hold if blood pressure <100/70]).
  - NMDA antagonists: Ketamine is the most potent nonopioid analgesic for opioid-tolerant patients. A brief infusion of 0.1–0.3 mg/kg IV over 15 minutes is followed by 0.1-0.3 mg/kg/hr IV infusion. In addition, magnesium is an NMDA receptor antagonist with analgesic and opioid-sparing effects (e.g., 30–50 mg/kg IV bolus followed by 6–20 mg/kg/hr IV infusion).
  - IV lidocaine: A bolus of 1.5 mg/kg can be followed by a 1–3 mg/kg/hr infusion. Contraindications include cardiac dysrhythmias and hepatic failure.
- Patients on MAT whose pain is not controlled with nonopioid approaches should be offered opioid analgesia; no patient should be denied adequate pain relief. Due to cross-tolerance and increased pain sensitivity, higher-than-typical doses of opioids should be anticipated.
- As with any patient receiving opioids, these patients should be monitored closely.
- For patients receiving buprenorphine for addiction treatment, consider treating acute pain with additional buprenorphine doses.
  - There is no clinical ceiling on buprenorphine for analgesia. SL buprenorphine can be given as frequently as every two hours. IV buprenorphine is a potent analgesic. Start at 0.3 mg IV and titrate as needed. Respiratory depression does occur at higher doses, but it has a ceiling effect that reduces the baseline by about 50%.
  - Buprenorphine is a partial agonist with a high affinity for the mu-opioid receptor. Thus, for patients receiving buprenorphine with severe acute pain for whom additional opioids are required, clinicians should select agents with affinity for the mu-opioid receptor sufficient to displace buprenorphine, such as fentanyl, sufentanil or hydromorphone.
- As a full opioid antagonist, naltrexone blocks the analgesic effects of most opioids. If naltrexone is still present and opioids are necessary, high-dose, high-potency opioids can be used to out-compete naltrexone at the opioid receptor. Patients must be closely monitored, at minimum with pulse oximetry and telemetry, to prevent oversedation and unintentional overdose.

SOURCE: Adapted from Project Shout.
For complete guide visit www.ColoradoMAT.org

Appendix XI

Acute Pain Management for Patients on Buprenorphine

CA BRIDGE
TREATMENT STARTS HERE

Acute Pain Management in Patients on Buprenorphine (Bup)* Treatment for Opioid Use Disorder

Medical/Surgical Units

James Gasper, PharmD, Andrew Herring, MD, Kyle Harrison, MD, Sky Lee, MD, Hannah Snyder, MD

Continue Maintenance Bup+
Split dose q4-8hrs
(e.g for total daily dose of 16mg = 4mg Bup SL QID)

Promote calm and comfort
Anxiety, fear, depression are common: Instill sense of control, provide education on self-management techniques such as mindful meditation. Reduce noise, uncertainty, confusion. Positioning, splinting, and physical comfort should be maximized. Minimize unnecessary NPO status.
Use adjunctive meds to treat symptoms (ie. diphenhydramine, ondansetron, melatonin, baclofen, etc).

Acetaminophen and NSAIDs
Schedule both around the clock if not contrainidicated.

Non-opioid analgesia

Gabapentinoids	**Alpha-2 agonists**
SNRI/TCA	**IV Lidocaine**
Regional Anesthesia	**Ketamine & Magnesium**

Additional opioids

Additional Bup
OK to increase dose and frequency for acute pain usual dose 24-32mg/day.

Full agonist Opioids
Can be added to maintenance Bup to provide synergistic analgesia. Titrate to analgesia and side effects. This will NOT precipitate withdrawal.

***Guidelines are for patients on maintenance Bup, however if patient is on maintenance Methadone or Naltrexone:**

- **Methadone:** Confirm maintenance dose. Continue full dose, can split dosing to aid pain control. Use multimodal analgesia. *Do NOT use Bup.*
- **Naltrexone:** If injectable, stop 1 mo prior to elective surgery and switch to PO. Stop PO 72 hours prior to elective surgery for full opioid agonists to be effective.

Gabapentinoids
Calcium channel inhibitors, gabapentin and pregabalin reduce postoperative pain and opioid consumption.

SNRI/TCA
Can help with neuropathic pain as well as anxiety/depression.

Regional Anesthesia
- Peripheral nerve blocks
- Spinal or Epidural anesthesia

Alpha-2 agonists
Clonidine and Dexmedetomidine are anxiolytic and analgesic with significant opioid sparing affects.

IV Lidocaine (Na channel antagonist)
Opioid sparing analgesic.

Ketamine & Magnesium (NMDA antagonists)
Ketamine is a potent non-opioid analgesic for opioid tolerant patients.
Magnesium also has analgesic and opioid sparing effects.

Guidelines are options for multimodal analgesic therapy. Use clinical judgement and avoid use if contraindicated.

NOVEMBER 2019

PROVIDER RESOURCES

California Substance Use Line
CA Only (24/7)
1-844-326-2626

UCSF Substance Use Warmline
National (M-F 6am-5pm; Voicemail 24/7)
1-855-300-3595

SOURCE: Bridge To Treatment

Appendix XII

Understanding Pain: A Complex Biopsychosocial Phenomenon

The United States is experiencing not only an epidemic of OUD, but also an epidemic of pain. Despite the fact that the United States consumes a disproportionately large fraction of the world's opioids, one-fifth of Americans suffer from pain. Pain, neuroscience and common sense agree, is not simply a process defined by receptors, neurological afferents and the interactions with the spinal cord and brainstem. Instead, it is an experience that incorporates all these biological elements and integrates them with psychological and social conditions to produce the experience of pain. To an extent not seen with other conditions, the biology of pain, the psychology of the patient and the social circumstances of a patient are intertwined and indivisible. Whether it is acute or chronic, easily treated or intractable, pain is a complex interplay of peripheral and CNS processes. The experience of pain is literally "all in the head," but it is hugely influenced by the context of a painful experience, past experiences of pain, genetics, mental health comorbidity, culture and patients' life experiences. One helpful model of conceptualizing pain is the biopsychosocial model, which incorporates elements of biology, psychology and social context into an understanding of the pain experience.

The Biology of Pain

Most physicians are aware of the distinctions between nociceptive pain, which can be somatic or visceral, neuropathic pain, inflammatory pain and types of pain less easily categorized, such as cancer pain, headache syndromes and fibromyalgic pain. Pain differs, too, in its duration, intensity, location and etiology. Sensorimotor pathways relay information about the nature of the pain stimulus. The cognitive and affective pathways incorporate sensorimotor information and evaluate it, integrating it with information based on prior experience and emotions. Because the biology of pain differs, treatments should be targeted wherever possible to the type of pain. Hospitalists are encouraged to use opioid-sparing multimodal analgesia as outlined in these guidelines, consulting pain specialists whenever pain is not well managed. Regrettably, the indiscriminate prescription of opioids may have contributed to an epidemic of chronic pain. Opioid-induced hyperalgesia[175-177] — in which sensitization of pronociceptive mechanisms occurs, resulting in a decrease in the pain threshold — may contribute to persistent pain for many patients.

Advances in the neurobiology of pain shed light on the physiological explanations for individual differences in pain thresholds and analgesic responses. While it goes without saying that every patient is different, fresh insights into the genetic and molecular basis of pain perception from model organisms and human twin studies underscore that there are significant genetic contributors and polymorphisms in pain tolerance and analgesic responsiveness.[178-180] Gender differences in pain processing are another important area of ongoing research, consistently demonstrating differences between males and females in pain threshold, susceptibility to chronic pain and analgesia sensitivity.[181] EEG studies, too, have identified measurable EEG signatures that predict differences in pain tolerance between individuals.[182]

The Psychology of Pain

Neuroimaging studies demonstrate the significant extent to which cognitive and affective factors impact the experience of pain. The anticipation of pain, attention or distraction, mood, catastrophizing and perceived control over pain can modulate peripheral, spinal and central nervous activity before, during and after a painful experience. The context of a painful stimulus and a person's prior life experiences greatly affect pain experiences.

For example: A woman who grew up loving dogs is at home with her new puppy. If she is suddenly nipped in the middle of the night with intensity "x," she will experience pain. However, her prior positive experiences with dogs, being safe at home and knowing the nip probably came from the puppy modulates her negativity of the experience. The same woman, who has always been wary of the ocean, is now at the beach. She had mustered the courage to swim when a lifeguard shouts "Shark!" If she feels a nip at her ankles with the same intensity "x," she will now have a drastically different pain experience. Expanding upon this example, a woman who loves dogs

will not be as upset by a mild dog bite as a woman who witnessed her father being mauled by a dog. Anticipation of pain, expectations surrounding painful experiences and expectations of relief impact the experience of pain on neuroimaging and by patient report. Studies of normal subjects demonstrate the power of both the placebo effect and the nocebo effect; the same noxious stimulus can produce markedly different neuroimaging and patient experiences. Accordingly, a host of psychological interventions have demonstrated evidence for relieving the negative effects of the pain experience. These include the use of supportive therapy, CBT, acceptance and commitment therapy, virtual reality therapy and mindfulness-oriented interventions that leverage insights into the cognitive and affective components of pain signaling.

Mental health and SUD are often major contributors to the experience of pain.[183] The association between mental and behavioral health disorders and chronic pain is well established. The vicious cycle of pain begetting depression and anxiety, which then impair a patient's effective management of his or her pain, is familiar to most physicians. Functional neuroimaging demonstrates shared neural mechanisms for pain, depression and anxiety.[184-186]

Finally, when pain is viewed as a cognitive, affective and sensory phenomenon, it is unsurprising that physician empathy has been identified as promoting pain relief.[187] The psychology of the patient-doctor interaction impacts the experience of pain and analgesia. Physician desensitization to patient pain complaints may play a significant role not just in undermining quality of care, but also in decreasing physicians' professional satisfaction.[188] When physicians recognize that treating pain can be emotionally draining, that self-awareness can help restore empathy. Physicians who find themselves frustrated in treating a patient with intractable pain may wish to consult with specialists in pain medicine and mental health.

Social Determinants of Pain

While few physicians are equipped to address the deeply rooted social factors that contribute to their patients' pain, it is important to understand that poverty, racism, social stress and isolation have been shown to affect patients' experiences of pain.[189] Pain, while universally experienced, is not universally understood. Patients, families and communities all value and understand pain differently. Types of pain can be influenced by social repercussions—genital pain, for example, is perhaps more isolating than back pain, as the former cannot easily be talked about with others. This isolation itself can intensify the pain experience. It is interesting to note that brain activation by social rejection or exclusion is very similar to that seen in physical pain. In an age of ever-widening income inequality and persistent racial disparities in health status, physicians are encouraged to know that the complex stresses of poverty and racism have studied, measurable impacts on pain perception.

The Biopsychosocial Model of Pain: Implications for Clinicians

The biopsychosocial model of pain underscores the importance of valuing and addressing each of these components when treating patients in pain. While a review of the state of pain neuroscience is beyond the scope of these guidelines, clinicians may wish to be aware that functional neuroimaging suggests there is far more interconnection between the sensory-discriminative and the cognitive-affective circuits than previously appreciated. The model in which "real" pain is biological and the psychological or affective components of pain are secondary and implicitly or explicitly perceived as less valid is inaccurate and misleading. Researchers theorize that the neural networks involved in pain processing may integrate the sensory, cognitive and affective aspects of pain into a "common currency," which gives rise to one unified pain experience.[190] To an extent not seen with other conditions, the biology of pain is the socio-psychology of pain. It is vital that physicians educate patients that the experience of pain is distinct for every individual and that the psychological and social determinants of pain are just as "real" to pain as tissue injury. Physicians and patients alike need to understand that all pain is "in our heads," and all pain deserves care.

Physicians serve their patients best when they recognize the complexity of pain and involve pain specialists, mental health providers, physical therapy and social workers for patients with complex pain presentations.

Appendix XIII

Cannabinoids and Pain

Cannabinoids and Pain: Counseling Patients

- As of this writing, no definitive, high-quality studies support the safety and efficacy of dispensary or pharmaceutical cannabinoids for analgesia in chronic noncancer pain. Until better evidence is available, physicians are discouraged from endorsing the use of cannabinoids for pain management. No evidence supports the efficacy of cannabinoids for acute pain. Patients may be counseled that research suggests that chronic use of cannabis may in fact complicate pain management.[219,220]
- It is recommended that any patient with chronic pain be encouraged to seek care from a pain medicine specialist.
- It is suggested that patients be counseled that the use of any drug that lacks rigorous FDA drug development and safety profiles carries inherent risks.
  - The testing and regulation of dispensary cannabis is poor to nonexistent.
  - Products purchased at dispensaries may be mislabeled, of undetermined content and/or contaminated with harmful substances.
  - It is important to remind patients that cannabis dispensary workers are not trained or qualified to give medical advice.
- Adverse effects associated with cannabinoid use include:
  - The development of cannabis use disorder (CUD)
    - Historically, one in 10 cannabis users — and one in six users under the age of 18 years — will develop CUD.[191,192]
    - Dispensary cannabinoid products available now are far more potent than those sold even a few years ago. Rates of CUD associated with use of potent dispensary cannabinoids may be as high as 30%.[193]
    - CUD is associated with an increased likelihood of developing other SUDs.[194]
  - Cognitive and behavioral
    - Short-term adverse effects include deficits in attention, memory and learning. Chronic use of cannabinoids may cause permanent cognitive deficits.[195,196]
    - Daily use or high doses of Δ9-tetrahydrocannabinol (THC) can cause anxiety, paranoia and psychosis. Chronic cannabis use is associated with an increased risk of developing schizophrenia.[197-206]
    - Cannabis use is associated with higher rates of depression, anxiety and suicidality.[207-209]
  - Cardiovascular
    - Smoking or vaping cannabinoids increases the risk for stroke and heart disease.[210-213]
  - Pulmonary
    - Smoking or vaping cannabis in any form can harm lung tissues, scar small blood vessels and expose patients to many of the same toxins, irritants and carcinogens found in tobacco smoke.[214,215]
    - Second-hand cannabis smoke is harmful to the health of exposed contacts, particularly children and adolescents.[216]
  - Malignancy
    - Chronic cannabis use may increase the risks of testicular cancer and human papilloma virus-related head and neck squamous cell carcinoma.[217,218]
- Pregnant or breastfeeding patients are strongly advised to avoid cannabis use due to known and unknown risks to the developing brain. The potential exists for birth defects, possible autism or spectrum disorders and other behavioral abnormalities in children of women who use cannabinoids in the perinatal period.[221]
- Despite the cautions above, medical clinicians may counsel their patients that many physicians, researchers, the AMA and the organizations represented in CO's CURE advocate for rigorous scientific research into the safety and efficacy of cannabinoids for pain management.

Introduction

The opioid epidemic has motivated physicians, researchers and patients to seek alternatives to opioids for the management of pain. Legalization and wider societal acceptance of cannabinoids, a broad term that describes the drugs derived from the plants of the genus Cannabis, has prompted some to ask whether cannabinoids might offer a safer, less-addictive alternative to opioid analgesia. While cannabinoids carry little risk of overdose death, their opioid-sparing potential and analgesic efficacy are unproven. Two ecological studies raised the possibility that medical cannabis legalization might reduce the use of opioids and rates of overdose death; however, subsequent individual-level research has challenged this hypothesis, and some states have seen rates of opioid-related harms increase after enactment of medical cannabis legislation.[222–224]

Research into the safety and efficacy of cannabinoids for analgesia has been largely limited to the study of chronic, neuropathic and cancer pain. Most of the existing studies of cannabinoids for medical use have been underpowered, unblinded or uncontrolled. A small number of observational studies of patients who use medical cannabis suggest that a subset of patients with chronic pain may successfully substitute cannabinoids for opioid analgesics.[225] Evidence regarding the efficacy of cannabinoids, including dispensary cannabis, for the management of acute pain is nonexistent. Despite the lack of persuasive data — and the significant adverse effects associated with cannabinoids — in vitro research, animal studies, preclinical experience and case reports suggest that the analgesic and opioid-sparing potential of cannabinoids warrant human studies with rigorous design, larger sample sizes and more consistent measures of outcome.[229,230,239]

Though cannabinoids have been studied for decades, the barriers to cannabinoid research are many. In particular, plant-derived cannabinoids in the United States are classified as Schedule I substances for which research is tightly regulated. Furthermore, the pharmacokinetics of these substances are complex and depend on the composition of the synthetic or herbal product and the route of administration. The chemical content of unprocessed botanical cannabis varies significantly; there are more than 100 pharmacologically active cannabinoids, the most widely studied of which are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). (The remaining cannabinoids and terpenes contribute to the smell, taste and possible pharmacologic effects of cannabis.)[226] The three FDA-approved cannabinoids — CBD (Epidolex), nabilone (Cesamet) and dronabinol (Marinol) — are isolated substances. The sale and possession of CBD products that contain no more than 0.3% THC (and thus lack psychoactive effects) are now legal under federal law.[227] While the AMA stands firmly against the legalization of recreational cannabis, it calls for "adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease."[228]

Evidence for Analgesic Properties of Cannabinoids

Well-described, shared neuropharmacological features and the substantial interactions of the mammalian endogenous cannabinoid system and endogenous opioid systems make an analgesic, opioid-sparing effect of cannabinoids physiologically plausible. [229–234] The human endocannabinoid system is composed of the cannabinoid receptors CB1 and CB2 and the endogenous human cannabinoids N-arachidonoylethanolamine (AEA), also known as anandamide, and 2-arachidonoylglycerol. CB1 receptors are concentrated in presynaptic neurons in areas of the brain that regulate appetite, memory, fear and motor responses, as well as in the spinal cord, dorsal root ganglia, the GI tract, liver, fat cells and skeletal muscle, while CB2 receptors are primarily found in macrophages and tissues that modulate inflammation.[207,235]

Both cannabinoid receptors and endocannabinoids are involved in the regulation of pain sensation, with modulatory actions at all stages of pain processing pathways.[236] The signal transduction systems of cannabinoid and opioid receptors are similar, and both are expressed in brain regions involved in antinociception, including the periaqueductal gray, raphe nuclei and central-medial thalamic nuclei.[230] Mu-opioid receptors and CB1 receptors are both found in the dorsal horn of the spinal cord at the first synaptic contact for peripheral nociceptive afferent neurons.[237,238] In vitro and animal studies provide ample evidence to support the analgesic effects of cannabinoids; some studies also suggest that these substances may work synergistically to enhance opioid analgesia.[229,230,239]

Most meta-analyses of cannabinoids and pain in humans are limited by small sample sizes and the wide heterogeneity of cannabinoid products, patient populations, outcomes and study designs. A 2018 systematic review of 104 studies (47 RCTs and 57 observational studies, of which 46 were low or very low quality, 43 were moderate quality and 15 were high quality, per Grades of Recommendation Assessment, Development and Evaluation) found moderate evidence of a 30% reduction in pain in patients using cannabinoids (29.0%) when compared with placebo groups (25.9%). The number needed to treat (NNT) to achieve a reduction in pain was 24. A 50% reduction in pain was reported by 18.2% of subjects in the cannabinoid groups compared to 14.4% in the placebo groups; however, these findings were statistically insignificant. The number needed to harm (NNH), notably, was 6. For comparison, the NNT for opioids is 4, and the NNH is 5. The authors note that the change in pain intensity seen with cannabinoids was equivalent to a 3-mm greater reduction on a 100 mm visual analogue scale when compared with placebo — well below the 30-mm threshold needed to represent a clinically significant difference. They acknowledge that their analysis is limited by the small sample sizes of the studies surveyed, with only 21 studies having more than 100 patients per treatment arm. They also note the short duration of most studies and observe that the efficacy of cannabinoids for pain appeared to wane over even a few days. The authors express concern that the short duration of most studies means that long-term adverse events, including the risk of iatrogenic dependence, cannabinoid tolerance and cannabinoid withdrawal syndrome, was not assessed by their review. They conclude that while cannabinoids show modest benefit for the treatment of some pain conditions, they are unlikely to be effective for the management of chronic noncancer pain given their high NNT and low NNH.[240]

These findings of the Stockings review closely mirror those of a 2018 Cochrane review (Mücke) of cannabinoids for the treatment of chronic neuropathic pain, which similarly concludes that "there is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain," while noting a high incidence of adverse effects.[241] A subsequent 2019 scoping review (Pratt) assessed data from 72 systematic reviews of medical cannabinoid use.[242] Notably, it judged only one review to be of high quality and highlighted the occurrence of adverse effects in more than 80% of patients taking cannabinoids, including 36% reporting serious adverse effects.[242] The authors conclude that while a small number of reviews suggested analgesic benefit with cannabis use, most were unable to draw conclusions due to inconsistent findings, and, finally, that the harms of cannabinoid use may outweigh potential benefits.[242] Until larger, more methodologically rigorous studies are conducted, the results of meta-analyses will be of limited value in guiding patients and clinicians.

Adverse Effects of Cannabinoids

Although the legalization of medical and recreational cannabis has likely led some patients to consider these compounds as generally safe, the studies discussed above note significant adverse effects with cannabinoid use, including dizziness, dry mouth, tachycardia, fatigue, somnolence, nausea, vomiting, disorientation, confusion, anxiety, cannabis hyperemesis syndrome, paranoia and hallucinations. A recent survey of Colorado EDs describes increased frequency of patient visits for significant cannabis-related adverse effects, including psychosis, suicidality, concomitant substance abuse, decrements in complex decision-making, motor vehicle collisions, cardiovascular and pulmonary complications, inadvertent pediatric exposures and hash-oil burn injuries (sustained when preparing drug concentrates). Contaminants found in cannabis can also expose users to infectious

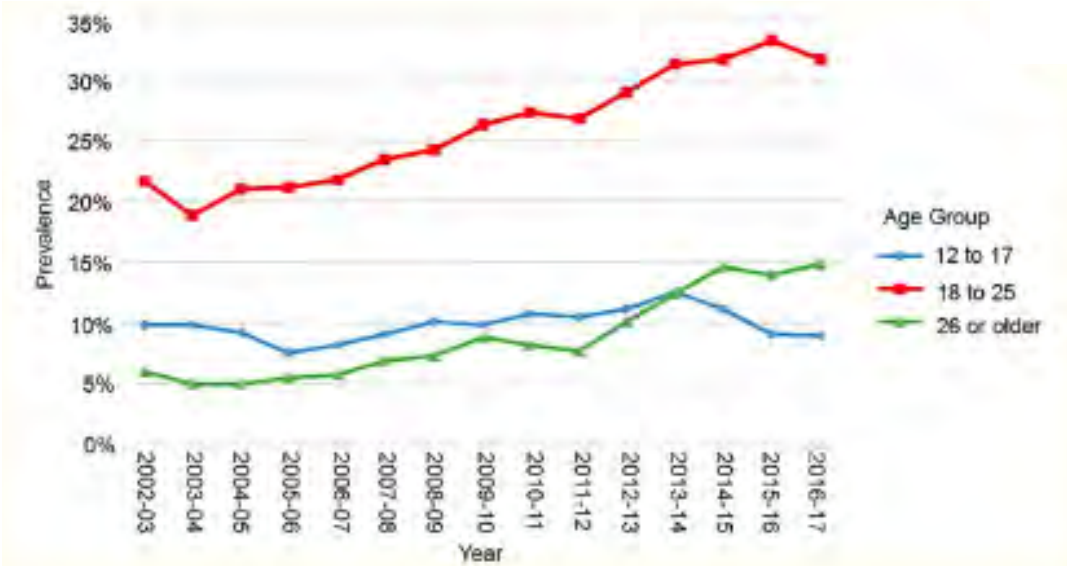
agents, heavy metals and pesticides.[243] A retrospective review of adolescent ED and urgent care visits found a significant increase in cannabis-associated visits.[244] Another retrospective review found significant increases in cannabis-related hospitalizations, ED visits and poison center calls in Colorado both after local medical marijuana policy liberalization and after local recreational legalization. Of note was the high prevalence of mental illness presenting in patient visits with cannabis-related codes, an association that warrants further investigation.[245]

While the long-term adverse effects of cannabinoids require further research, a number of studies have associated THC exposure with the later development of schizophrenia,[197–206] depression,[208,210] anxiety[207] and suicidal ideation, attempts and completion.[209] A large prospective cohort study also linked cannabis use to a substantial risk for the later development of CUD,[246] estimating that 9% of adults and 17% of adolescent users will develop the disorder.[191] Both grey- and white-matter changes have been found in chronic cannabis users, as have volume reductions in the amygdala and hippocampus.[195,247–250] National reporting systems and rigorous research into the short- and long-term adverse effects of cannabinoids are urgently needed.

Clinicians in Colorado are likely aware of the high incidence and prevalence of cannabis use in the state **(TABLE 1)**. An estimated 39% of patients who receive chronic opioid therapy for pain report also using cannabis.[251,252] When the opportunity arises, clinicians are encouraged to advise patients that current evidence does not support the use of cannabis as a safe, effective analgesic and that further research is warranted. It is recommended that patients with chronic pain who inquire about cannabis for analgesia be referred to a pain management specialist.

(TABLE 1)

Cannabis Use In the Past Month In Colorado



SOURCE: Reproduced from Substance Abuse and Mental Health Services Administration National Survey on Drug Use and Health: State Estimates. Available at https://pdas.samhsa.gov/saes/state. Accessed November 2018

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