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

The Colorado Chapter of the American College of Emergency Physicians

2020 Opioid Prescribing and Treatment Guidelines

Developed by Colorado ACEP 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
c|h|a Colorado Hospital Association

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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

Emergency Physician Editors

Dylan Luyten, MD, FACEP
Ashley Morse, MD
Erik Verzmeniks, MD, FACE
Steve Young, MD

Associate Editors

Elizabeth Esty, MD
John Spartz

Section Editors

Robert Valuck, PhD, RPh, FNAP
Introduction and The Opioid Epidemic in Colorado
Erik Verzemnieks, MD, FACEP
Limiting Opioid Use in the Emergency Department
Rachael Duncan, PharmD, BCCCP
Charleen Gnisci Melton, PharmD, BCCCP
Donald E. Stader III, MD, FACEP
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

Copy Editors

Paula Benson
Julie Denning
Rachel Donihoo

Task Force Chair

Erik Verzmeniks, MD, FACEP

Task Force Members, Volunteers and Other Contributors

Travis Barlock, MD
Kevin Boehnke, PhD
Jon Clapp, MD
Will Dewispelaere
Kenneth Finn, MD
Chris Johnston, MD
Kevin Kuachar, PharmD
Emily Lampe, MD
Judy Lane, MD
Julia Luyten
Rachael Rzasa Lynn, MD
Jeffrey Wagner, MD
Helena Winston, MD
Narin Wongngamnit, MD

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Introduction

Medical providers 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 aged 50 years or younger.[1] Correspondingly, hospital visits for opioid-related adverse drug events (including accidental overdose and prolonged opioid use), 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 2001,[2] and another 130 Americans are dying every day (**FIGURE 1**).[3]

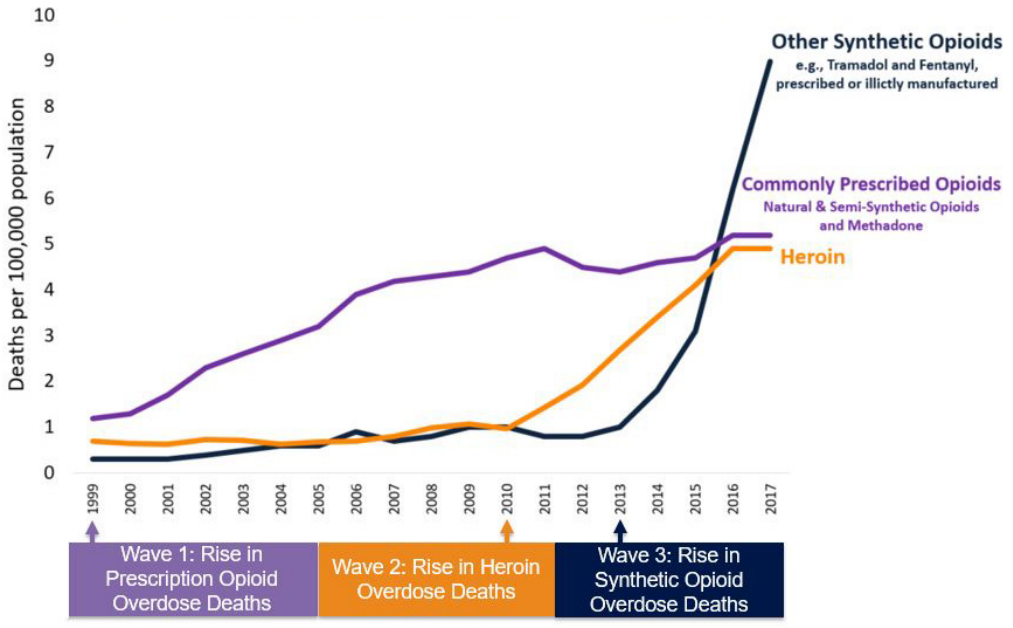
More than 10.3 million people over the age of 12 years self-reported misusing opioids in 2018 (9.9 million misused prescription pain relievers and 808,000 used heroin).[4] The pharmaceutical use of opioids skyrocketed between 1990 and 1996; prescriptions for fentanyl rose 1,000%, followed by morphine (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 period.[5] In 2017, 58 opioid prescriptions (for an average length of 18 days) were written for every 100 patients in the United States.[6]

The dire consequences of the widespread availability of prescription opioids emerged over time. The "lag period" between a patient's first exposure to an opioid (either medical or nonmedical) and their first treatment admission is an average of seven years. For patients who die of an overdose, the time between first exposure to an opioid and death is between nine and 13 years.[7,8] In 2017, opioids were responsible for 34% of all substance abuse treatment admissions for patients aged 12 years and older.[9]

The financial implications of this epidemic are equally staggering. The nonmedical use of opioid pain relievers cost society approximately $1 trillion between 2001 and 2016; unless major changes are made, the financial impact is projected to grow by another $500 billion by 2020 (**FIGURE 2**).[10]

(FIGURE 1)

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

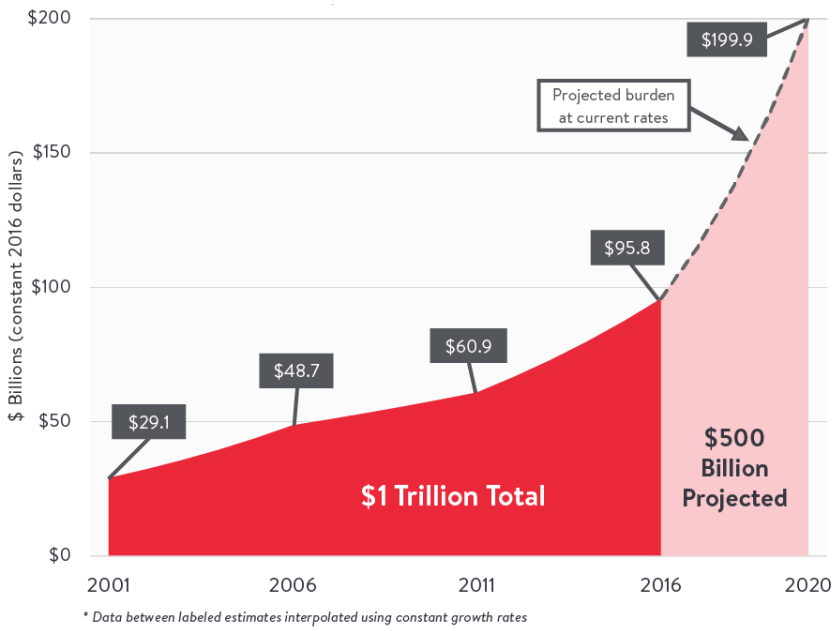


SOURCE: CDC MMWR[2]

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 liberal use of these potentially lethal drugs, the medical community is compelled to acknowledge its role in creating this crisis. However, it also has the power to reverse these grim statistics by reforming its practices with resolve and innovation.

These guidelines are meant to inform and augment clinical judgment, not replace it. Although CO's CURE acknowledges the value of opioids in certain clinical situations, including the treatment of sickle cell pain, hospice, severe trauma, burn and cancer pain, it advocates using extreme caution in all cases.

These guidelines are a compilation of ideas and suggestions that can be implemented by clinicians and hospitals to improve patient care in the context of the opioid epidemic. Adopting these guidelines in their entirety is not necessary, or often feasible in many hospitals. Rather, each hospital and clinician should consider which of these suggestions are most appropriate given the unique processes and resources of the hospital, and should have them reviewed by legal counsel and compliance leaders. The suggestions in these guidelines should not be viewed as a substitute for clinical judgment or obtaining legal counsel particularized to the hospital's situation.

The Opioid Epidemic in Colorado

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

2017 Colorado Statistics

- More than 3.7 million opioid prescriptions were dispensed to one million patients (**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 overlapped the use of opioid and benzodiazepine prescriptions.[13]
- According to data from the Colorado Prescription Drug Monitoring Program (PDMP), 671.3 opioid prescriptions were filled per 1,000 residents.[13]
- There were 134.3 treatment admissions for heroin per 100,000 Coloradans and 40.6 treatment admissions for pharmaceutical opioids per 100,000 residents.[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
Data Source: Colorado Prescription Drug Monitoring Program, Colorado Department of Regulatory Agencies Analysis by: Colorado Department of Public Health and Environment, 2018

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]

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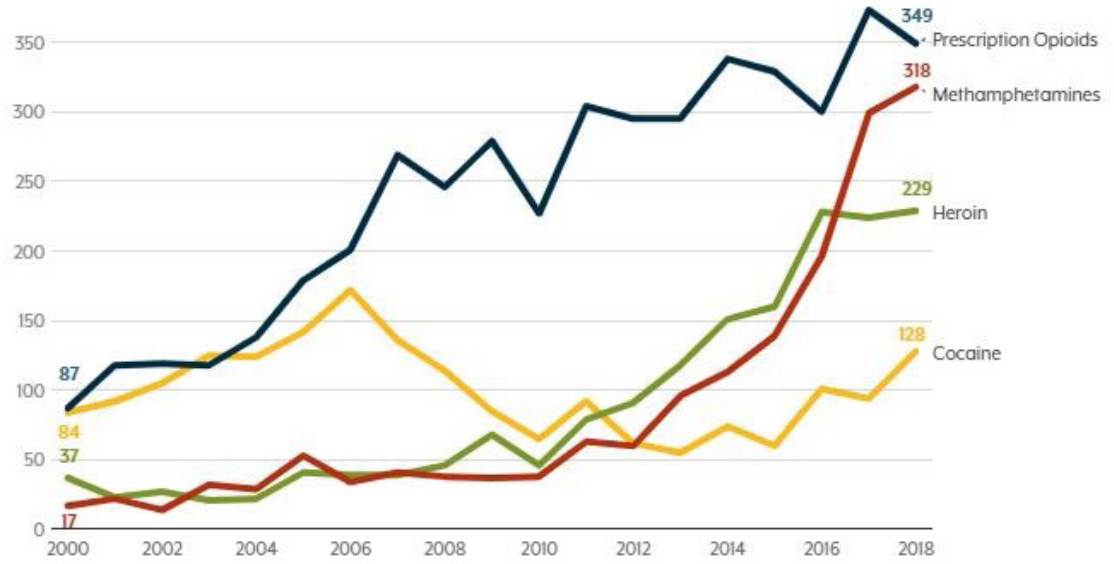
(FIGURE 3)

Number of Drug Poisoning Deaths 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]

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 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] Despite this hindsight perspective, 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 these drugs 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]

Introduction continued

CO's CURE

Faced with the greatest public health crisis of a generation, Colorado is taking a stand for the benefit of all. CO's CURE is the nation's first set of comprehensive, multispecialty medical guidelines designed to end the opioid epidemic. The unique structure of these evidence-based recommendations is anchored by objectives that can be shared by all medical specialties. The four pillars of CO's CURE:

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 (ACEP) and published as part of Colorado ACEP's *2017 Opioid Prescribing & Treatment Guidelines.* Emergency physicians can take pride in the fact that their specialty has helped initiate a movement across the entire house of medicine. When implemented in 10 Colorado emergency departments (EDs) as part of the Colorado Opioid Safety Pilot done by Colorado Hospital Association (CHA), the approach entailed in these guidelines resulted in a 36% decrease in opioid use and a 31% increase in the use of opioid alternatives for pain management over a six month period.[26]

Now is the time for all specialties and clinicians to unite to create better treatment paradigms for the benefit of patients and communities. Together, clinicians can and will end this crisis.

Limiting Opioid Use in the Emergency Room

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Limiting Opioid Use in the Emergency Room

The majority of patients who develop OUD report that their first exposure to an opioid involved a pain medication prescribed to them or diverted from a family member or other contact.[27] Reducing the potential for the societal and economic burdens created by these exposures starts with judicious opioid prescribing practices. When used appropriately, opioids are effective and essential analgesics worthy of their role as a mainstay of emergency medicine practice. An excessive reliance on these powerful medications, however, places patients in unnecessary danger and increases the risk of dependence, misuse and the development of OUD. The human and economic consequences of aberrant opioid use are clear: higher medical expenditures, prolonged hospital stays and substantial use of health care resources.[28]

Pain is the most common reason patients visit EDs in the United States.[29,30] Of the estimated 145.6 million ED visits in 2016, nearly 45% were attributed to pain; between 17% and 21% of these patients were prescribed an opioid upon discharge.[31-33] It is important to note that while emergency physicians write an estimated 4.8% of the country's opioid prescriptions,[34] these prescriptions are for shorter durations and smaller quantities of immediate-release formulations than opioid prescriptions dispensed by non-ED providers.[33] Prescriptions provided to opioid-naive patients in the ED are more likely to align with CDC recommendations than those written by primary care physicians and have been associated with a lower risk of long-term use.[35]

Although the number of opioid prescriptions administered in the ED increased dramatically in the first decade of the millennium, mirroring the rise in opioid prescriptions across all specialties, emergency clinicians were among the first to respond to the national opioid crisis.[31] Emergency physicians have demonstrated one of the largest decreases in total opioid prescription (8.9%) of all subspecialties in the period 2007-2012.[36,37] Emergency physicians in Colorado have led efforts to protect their patients and communities from the risks associated with inappropriate opioid use. In 2017, CHA launched the Colorado ALTO Project, a program that was based on Colorado ACEP's first iteration of opioid prescribing guidelines, that has since trained more than 95% of EDs in the state in ALTO protocols.

Across all specialties, a commonsense approach to addressing the epidemic of OUD and overdose deaths includes decreasing the frequency and ease with which opioids are dispensed. Emergency physicians can play a vital role in screening patients, prescribing opioids judiciously, maximizing the use of multimodal analgesic techniques and ALTOs and providing patients with thorough counsel on the risks of diversion, misuse and dependency prior to discharge.

Practice Recommendations

Limiting Use of Opioid Therapy in the ED

1. **Opioids are inherently dangerous, highly addictive drugs with significant abuse potential, numerous side effects, lethality in overdose, rapid development of tolerance and debilitating withdrawal symptoms. Emergency physicians are encouraged to reserve opioids for the treatment of pain that has not responded to nonopioid therapy and for patients in whom nonopioid therapy is contraindicated or anticipated to be ineffective.**
   a. Opioids are among the three broad categories of medications that present abuse potential, 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. The resultant spike in dopamine not only reduces the perception of pain, it 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; greater amounts are required over time as the patient grows increasingly immune to the drug's effects.[38] This mechanism also contributes to the high risk of overdose following a period of abstinence.[39] Tolerance can be lost in times of sobriety, leading relapsed users to take a previously "safe" dose with disastrous results.[40] The effects of opioids are also mediated by specific subtype opioid receptors (mu, delta and kappa) that are 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.

Limiting Opioid Use in the Emergency Room continued

c. Besides the significant abuse potential, rapidly developing tolerance and agonizing withdrawal symptoms that accompany opioids, patients also experience serious side effects, including drowsiness, mental confusion, constipation and nausea (**TABLE 3**).[41] These complications, which often necessitate additional medical care, can prevent patients from performing daily tasks and remaining active in the workforce.

(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 • Sudden cardiac death with the concomitant use of benzodiazepines and methadone • Hormonal disruptions, including decreased testosterone in males • Decreased luteinizing hormone, follicle-stimulating hormone, and fertility in women • Musculoskeletal compromise, including an increased risk of osteoporosis • Immunosuppression • Inhibition of cellular immunity via delta and kappa receptors • Hyperalgesia (i.e., upregulation of receptors and increased tolerance) • Sleep disturbances (e.g., shortened deep sleep cycle) • Delayed or inhibited gastric emptying, increased sphincter tone, and blockade of peristalsis

SOURCE: Martin PR, Hubbard JR. Substance-related disorders. In: Ebert MH, Loosen PT, Nurcombe B: Current Diagnosis & Treatment in Psychiatry. New York: McGraw Hill; 2000:233-259.

(TABLE 4)

Signs and Symptoms of Opioid Intoxication and Withdrawal

Intoxication	Withdrawal
• Activation or "rush" with low dosages) and sedation/apathy (with high dosages)	• Depressed mood and anxiety; dysphoria
• Euphoria	• Dysphoria and cravings
• Feelings of warmth, facial flushing, or itching	• Piloerection, lacrimation, or rhinorrhea
• Imparied judgement, attention, or memory	• Frequently, "high" attention
• Analgesia	• Hyperalgesia; joint and muscle pain
• Constipation	• Diarrhea and gastrointestinal cramping, nausea, or vomiting
• Pupillary constriction	• Pupillary dilation and photophobia
• Drowsiness	• Insomnia
• Respiratory depression, areflexia, hypotension, tachycardia	• Automatic hyperactivity (e.g., hyperrelexia, tachycardia, hypertension, tachypnea, sweating, hyperthermia)
• Apnea, sedation, coma	• Yawning

SOURCE: Martin PR, Hubbard JR. Substance-related disorders. In: Ebert MH, Loosen PT, Nurcombe B: Current Diagnosis & Treatment in Psychiatry. New York: McGraw Hill; 2000:233-259.

Limiting Opioid Use in the Emergency Room continued

2. Prior to administering or prescribing an opioid, emergency physicians are encouraged to perform a risk assessment to screen for abuse potential and medical comorbidities.

a. Multiple agencies, including the CDC and Colorado Department of Regulatory Agencies, advocate using a screening instrument, such as the Opioid Risk Tool, to evaluate for factors that might predispose patients to addiction and misuse. While this approach has only been validated in patients with chronic pain, such screening tools may help emergency medicine clinicians identify high-risk patients.[43,44] (**SEE APPENDIX V**)

b. Emergency clinicians should be aware that no validated screening tools exist for the identification of patients at low risk for developing OUD. It is important to consider the potential vulnerability of every patient.
   i. A recent review of patient characteristics and screening tools for predicting risk of prescription opioid addiction concludes that patients with a history of substance use disorder (SUD), pain disorders, personality disorders, somatoform disorders or psychotic disorders have the highest relative risk for OUD.[45] It also concluded that the use of atypical antipsychotic and anxiolytic agents confers excess risk.[45] Only the absence of a mood disorder is associated with a lower risk of developing OUD.[45]

c. Risk factors for the development of OUD include:
   i. Personal or family history of any SUD (e.g., alcohol, nicotine, illicit drugs, prescription drugs)[46]
   ii. History of any pain disorder[47,48]
   iii. Age between 16 and 45 years
   iv. Mental health/psychological history (particularly mood and personality disorders, somatoform disorders and psychotic disorders); anxiety and mood disorders confer a moderately increased risk.[45]
   v. In addition, emergency clinicians are advised to consider comorbid health conditions and exercise caution when prescribing opioids to those at increased risk for adverse drug reactions and accidental overdose.[46]

d. High-risk medical comorbidities and risk factors include:
   i. Pulmonary disease (e.g., chronic obstructive pulmonary disease (COPD), sleep apnea)
   ii. Cardiovascular disease (e.g., congestive heart failure)
   iii. Organ dysfunction (e.g., renal or hepatic failure)
   iv. Elderly age
   v. Combination therapy with other opioids or sedating agents

3. Emergency medicine physicians are encouraged to consult the PDMP to assess for a history of prescription drug abuse, misuse or diversion, as well as potential drug interactions.

a. 2014 Colorado House Bill 14-1283 requires all Colorado-licensed prescribing practitioners with Drug Enforcement Agency (DEA) registrations to create an account with the Colorado PDMP.[49]

b. Drug monitoring programs have been shown to influence opioid prescribing practices, especially in cases of lost or long-term prescriptions.[50]

c. These programs can help clinicians identify patients with multiple recent prescriptions from various clinicians (i.e., “doctor shopping”) and help spot those already using other controlled medications on a chronic basis.[51]

d. Although there is limited data to indicate the impact of PDMPs on patient outcomes, these programs can provide critical opportunities for intervention through a referral to support services, the initiation of medication for addiction treatment (MAT) and further consultation with a pain management or addiction specialist.

e. Along with information gathered from drug monitoring programs, concerns about a possible OUD, misuse or diversion should prompt further conversations between the physician and patient regarding the adverse effects of opioid use.

f. Information gathered from PDMPs should not preclude the use of opioids for the treatment of acute pain in the ED, but this data should be considered when weighing the risks and benefits of opioid therapy.

Limiting Opioid Use in the Emergency Room continued

4. **The use of opioid analgesia can be detrimental for the treatment of uncomplicated back pain, dental pain, cyclic vomiting and headaches. Opioids should generally be avoided in patients with these conditions and only administered in the rare circumstance that alternative treatments have failed or are contraindicated.**
   a. Numerous studies have shown the superiority of opioid alternatives, including scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (APAP), for both uncomplicated back and dental pain.[52,53]
      i. Despite this, a significant number of patients who present with these complaints receive opioids at discharge (approximately 50% of those with dental pain and 39% with lower back pain).[54]
         1. A secondary analysis of data from all patients visiting an ED with a toothache or other dental complaint from 2013 to 2015 found that 2% of visits were for dental pain.[55] Forty-four percent of these patients received an analgesic in the ED, including opioids (31%), NSAIDs (5%), APAP (5%) and/or a local anesthetic (6%). On discharge, 64% were prescribed an analgesic; 54% received an opioid, 20% were prescribed NSAIDs and 5% received APAP.[55] The authors note that the excessive reliance on opioids and the underutilization of NSAIDs, APAP and local anesthetics represent a clear opportunity to improve the management of dental pain in the ED.[55]
         2. A survey of Medicaid data from the same time period found that ED clinicians were more than four times more likely to prescribe opioids to patients with dental conditions. Approximately 38% of patients who received care in the ED filled an opioid prescription, compared with 11% whose complaints were managed by a dentist.[56]
      ii. Opioids are associated with decreased function at six months and prolonged disability at one year in patients with uncomplicated lower back pain.[57,58]
   b. For cyclic vomiting syndrome, continued use of opioid therapy is a poor prognostic marker that may contribute to disease coalescence. Dependence and withdrawal are also associated with recurrent episodes.[59]
   c. Opioids have deleterious effects when used to treat headaches and should be avoided. Potential complications include the precipitation of medication-overuse headaches, anxiety, disability and depression.[60] Opioids are also associated with the progression of migraine headaches from acute to chronic.[61]
      i. Opioids are not as effective as standard treatments for the management of headaches and can render acute migraine medications less efficacious.[62,63]
      ii. The American Academy of Neurology, American Headache Society and ACEP caution against the use of opioids for headache treatment. These agents are best reserved for extraordinary situations in which all other options fail or are contraindicated.[64,65]
         1. Furthermore, the American Academy of Neurology has made opioid reduction for the treatment of migraines a focus of its *Choosing Wisely* campaign.[66]

5. **Emergency physicians are discouraged from adjusting opioid dosing regimens for chronic conditions and prescribing opioids for acute exacerbations of chronic noncancer pain. This includes administering "one-time" doses in the ED.**
   a. Long-term opioid medication regimens are best managed by a single provider outside the acute care setting, typically a primary care provider or pain specialist. In the rare instance that a patient's drug regimen must be adjusted in the ED, it is best done in direct collaboration with the patient's outpatient opioid prescriber.

b. Emergency physicians are cautioned against initiating or adjusting opioid prescriptions for the treatment of chronic pain.[67]
   i. Clinicians often require patients with chronic pain to sign an opioid contract, which may mandate the use of a single prescribing provider and pharmacy.[68] It is important to honor these agreements, which frequently provide guidance for emergency medicine clinicians and outline steps the patient can take to manage acute exacerbations of pain.
   ii. Emergency medicine clinicians are discouraged from refilling or prescribing opioid medications for patients taking opioids for chronic noncancer pain.
   iii. It is advised that clinicians avoid administering "one-time" doses of parenteral or oral opioids for acute exacerbations of chronic pain, regardless of whether a patient is prescribed an opioid at discharge.
   iv. If the patient is not being seen by a pain specialist, a referral should be initiated.
   v. Nonopioid treatments are encouraged for acute exacerbations of chronic noncancer pain (see section on ALTO for the Treatment of Pain).

6. EDs are advised to remove pre-populated doses of opioids from their computerized provider order entry systems.

a. Computerized provider order entry is an integral part of current ED practice. As part of almost every electronic health record (EHR) system, order sets have become a popular mechanism for decreasing clicks, standardizing care and meeting clinical metrics. As they pertain to the use of opioids, many order sets pre-populate doses of opioids for pain, including additional "as-needed" doses.
b. Avoid using default or automatic opioid doses. Removing default quantities from electronic order entries appears to decrease the number of opioids prescribed and thus dispensed.[69,70]
c. Treating clinicians are advised to prescribe opioids only after the risks and benefits of appropriate use have been thoroughly considered.
d. Order sets with pre-populated opioid doses may expose patients to risk by dispensing these drugs automatically based on individual complaints.
e. According to the Institute of Safe Medication Practices, order sets that contain multiple opioids, multiple doses or multiple routes of administration can increase the risk of unintentional hospital opioid overdose.[71]

Minimizing Harm with Opioid Administration and Discharge Prescribing

7. Emergency medicine clinicians are encouraged to use the oral route of administration whenever possible. Intravenous (IV) opioids may be best reserved for patients who cannot consume food or medications by mouth, in cases of suspected GI malabsorption or when immediate pain control or rapid dose titration is necessary.

a. Oral formulations are preferable due to their longer duration of action and reduced risk of adverse events. Parenteral formulations pose a greater risk of side effects, medication errors and euphoria, which may increase the potential for addiction.[72-75]
b. In general, the more rapid an opioid's onset, the greater potential for addiction. (IV onset is five to 10 minutes on average, compared to 15-30 minutes for oral administration).[76]
c. Furthermore, the duration of action is greater with oral administration than with IV administration, a factor that may enable more consistent pain relief and less frequent dosing.

Limiting Opioid Use in the Emergency Room continued

8. **Emergency medicine clinicians are encouraged to avoid the coadministration of opioids with barbiturates, benzodiazepines and other CNS depressants.**
   a. This combination can increase the risk of opioid-related adverse events.
   b. Patients taking opioids and benzodiazepines together have 10 times the risk of fatal overdose than those taking opioids alone.[77] The concomitant prescribing of opioids for a patient taking benzodiazepines increases the risk of unintentional overdose, respiratory depression and death.[67]
   c. Other medications with CNS-depressant properties include, but are not limited to, nonbenzodiazepine sedative-hypnotics, muscle relaxants, sedating antidepressants, antipsychotics and antihistamines.[78-80]
   d. Patients who take multiple opioid prescriptions at higher doses are also at a significant risk of overdose; the concurrent use of multiple opioid medications is discouraged.[81]

9. **It is important to understand that tramadol is not a "safe" opioid. The drug carries significant side effects and has been associated with higher rates of long-term opioid use.**
   a. Tramadol (Ultram) binds weakly to u-opioid receptors after undergoing conversion to its active metabolite O-desmethyltramadol by CYP2D6. The drug also has serotonin-norepinephrine reuptake inhibitor (SNRI) activity among several other mechanisms of action. Wide variations in the pharmacogenetics of tramadol metabolism can result in significant individual differences in concentrations and analgesic effect.[82]
   b. Widely viewed as a "less potent" opioid, clinicians often prescribe tramadol for acute pain in an attempt to avoid "stronger" medications. Tramadol is a Schedule IV drug, a factor that may help reinforce this assumption. Unfortunately, not only does tramadol carry additional side effects, including seizures and significant drug-drug interactions not seen with other opioids, the medication also appears to pose a significantly greater risk of long-term opioid use.
      i. Tramadol has been associated with an elevated risk of long-term opioid use at one and three years compared to other opioids.[83]
      ii. Additional studies have identified higher rates of adverse events, including overdose, among teenagers taking tramadol.[84]
      iii. Much higher rates of long-term opioid use were found in a cohort of opioid- naive patients receiving tramadol after elective surgery compared to those prescribed other short-acting opioids.[85]

10. **When opioids are prescribed, emergency physicians are encouraged to administer the lowest possible dose for the shortest duration possible, typically no more than three days.**
    a. The pharmacological potency of an opioid is largely determined by the dose prescribed.
    b. The duration of any opioid prescription should be as short as possible (ideally, no more than three days for any acute painful condition).[86,87]
    c. Opioid dependence is demonstrated in as little as three days, and there is an association between long-term opioid use and initial prescriptions of longer duration.[83,88,89]
    d. It is well documented that persons who abuse opioids nonmedically often get them from friends and families, so it is essential to judiciously limit the quantity of opioids administered at discharge.[90]
    e. Even small-quantity prescriptions can result in unused pills. An estimated 49% of patients prescribed opioids on discharge from the ED report having unused pills 14 to 21 days later; approximately 9% never fill their opioid prescriptions at all and one-third of the pills prescribed remain unused.[91]
    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 refill.[92]
    g. Acute pain lasting longer than seven days after the appropriate treatment of any existing underlying conditions should prompt a re-evaluation of the working diagnosis or management approach. To prescribe further opioids to the same patient, clinicians are required (per SB 18-022) to review the PDMP for other problematic prescriptions.[92]

Limiting Opioid Use in the Emergency Room continued

11. Emergency medicine physicians are discouraged from represcribing lost or stolen opioid prescriptions.

a. In general, clinicians are advised to avoid rewriting opioid prescriptions that have been lost or stolen.

b. There may be certain circumstances (e.g., an accompanying police report) in which replacing a prescription for a controlled substance may be warranted; however, it is recommended to discuss the refill request with the patient's primary prescribing provider before proceeding.

12. Emergency medicine physicians are discouraged from prescribing or administering long-acting and extended-release opioid formulations.

a. Long-acting and extended-release opioids are indicated only for chronic pain and should not be used for the treatment of acute or intermittent symptoms.[93]

b. These agents are especially dangerous in opioid-naive patients, even at recommended dosages, and carry a long-term risk of dependence that is nearly 4.5 times higher than that of immediate-release formulations.[83]

c. ED patients may have fluctuating renal and liver function levels and rapidly changing analgesic needs that may affect dosing.

d. Exceptions exist for patients taking long-acting or extended-release formulations for the treatment of addiction or chronic pain. Rapid discontinuation of these agents is discouraged; as such, the administration of opioids may be necessary to meet the baseline requirements of patients with extended stays in the ED. (**SEE APPENDIX X, MANAGING ACUTE PAIN IN PATIENTS ON MAT.**)

13. Emergency clinicians are encouraged to educate patients and caregivers about the potential long-term risks and immediate adverse effects of opioid therapy.

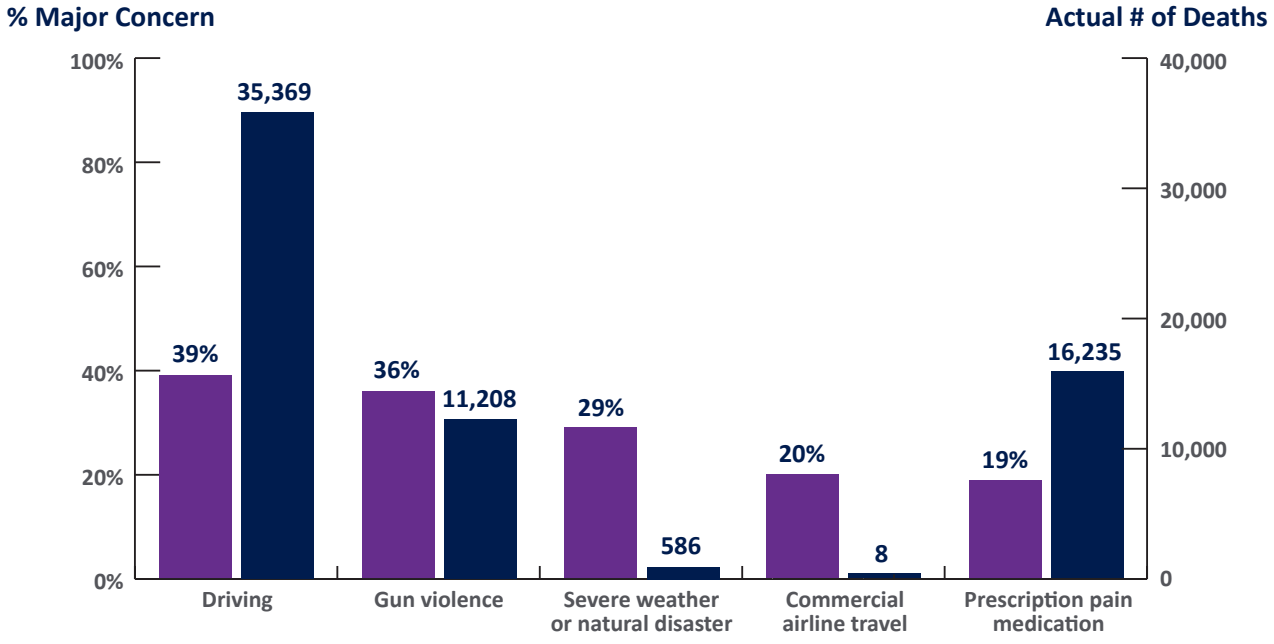
a. Patients are often unaware of the risks associated with opioid medications and uninformed about the equally effective ALTOs available for analgesia.

b. Evidence suggests that clinicians do a poor job of educating patients on the risks of opioids (**FIGURE 4**). Fewer than one in five Americans consider prescription pain medication to be a serious safety threat.

(FIGURE 4)

Public Perception of Opioid Risk

Only 1 in 5 Americans consider prescription pain medication to be a serious safety threat



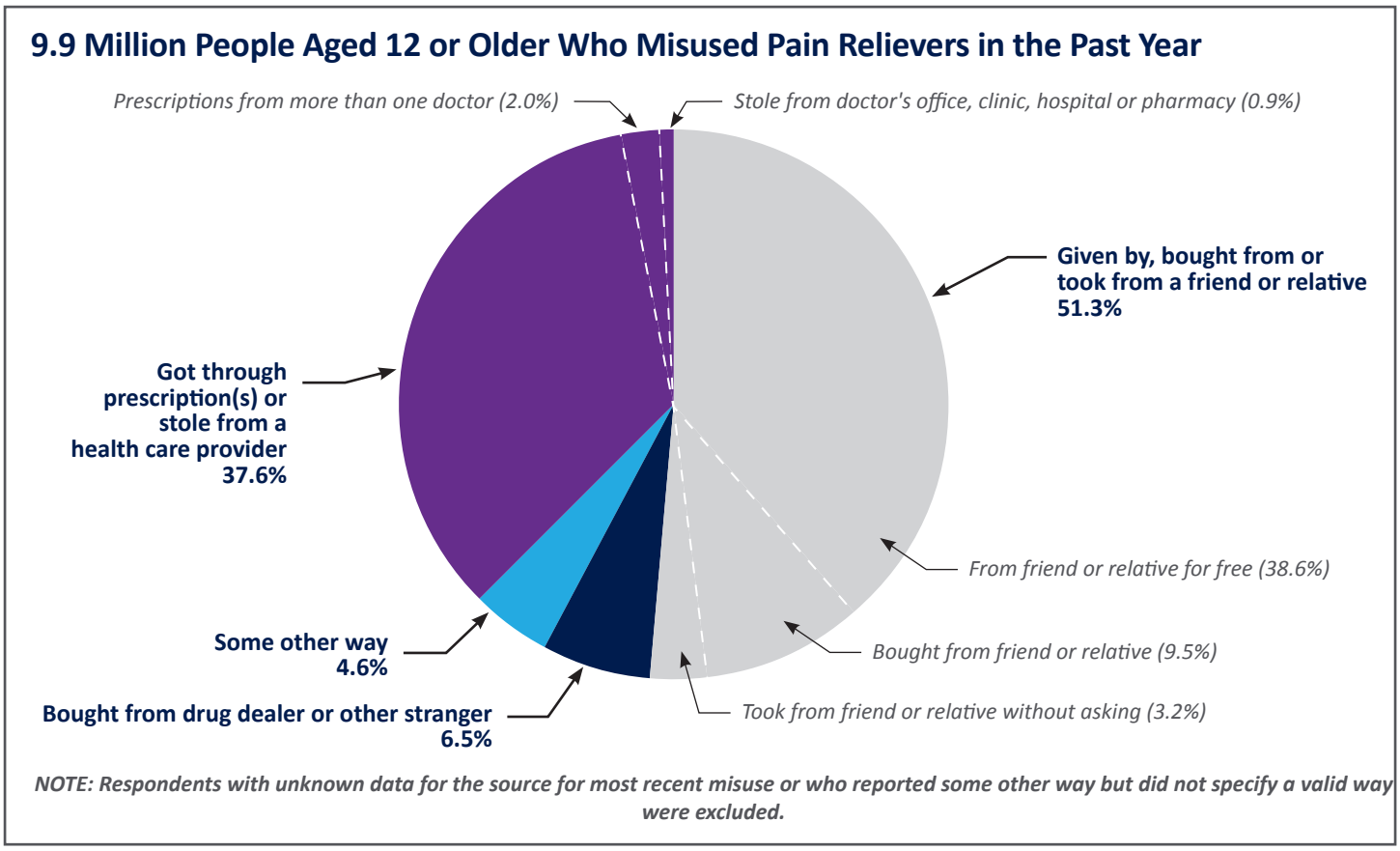
Limiting Opioid Use in the Emergency Room continued

c. Clinicians are encouraged to inform their patients about the risks and adverse effects of opioid medications as well as alternative pharmacologic and nonpharmacologic multimodal analgesic options.
d. More than 50% of ED patients discharged with opioid prescriptions admit to misusing them in the 30-day period following their visit.[47]
e. In addition, nearly 80% of new heroin users between the ages of 12 and 49 years report the previous nonmedical use of prescription opioids.[48]
f. All patients are at risk for opioid misuse and abuse. The National Safety Council estimates that more than half of U.S. patients have at least one risk factor for developing OUD. A prior history of substance abuse, the use of psychotropic drugs and younger age increase this potential; however, even an opioid-naive patient with no risk factors can develop dependence.[49,50]
g. It may be beneficial to remind patients that they may request nonopioid multimodal analgesia in lieu of opioids, even for severe pain.

14. Educate patients on the risks posed by unsecured opioids and provide instructions on the proper storage and disposal of these medications.

a. More than 50% of nonmedical opioid users obtain these medications from family members or friends or through illicit purchase.[4]
b. The CDC advises prescribers to discuss the risks that opioids can pose to household members and other individuals if intentionally or unintentionally shared or diverted. It is also important to emphasize the fact that others can experience an overdose at the same or lower dose than that prescribed for the patient.
c. It is strongly encouraged that patients be educated on safe opioid storage. TakeMedsSeriously.org is an excellent resource for patients and families. Specifically, encourage patients to consider the following:
    i. Avoid storing opioids in obvious places like bathroom cabinets or on kitchen counters, where others might find them.
    ii. Store medication out of reach of children.
    iii. Keep track of the quantity of opioids they consume.
    iv. Consider filing a report with the police if opioid medication has been stolen.
    v. Remember that sharing or selling opioids with another individual is a felony.
d. Patients are encouraged to use community prescription drug take-back resources whenever possible.
    i. The Colorado Department of Public Health and Environment's (CDPHE) Colorado Household Medication Take-Back Program provides instructions for safe disposal and information on safe disposal sites.
    ii. Mail-back envelopes are available at some pharmacies.
    iii. Patients who are unable or unwilling to access take-back resources can be instructed to mix their unused opioids with an inedible substance (e.g., kitty litter, coffee grounds, sawdust). The unused pills should then be sealed in a plastic bag, wrapped in newspaper or a brown paper bag and placed in the trash on the day of trash pickup.
    iv. To minimize their impact on the environment, unused medications should never be flushed down a toilet or drain.

Limiting Opioid Use in the Emergency Room continued



SOURCE: SAMHSA NSDUH 2018[4]

15. Patients receiving controlled medication prescriptions should be able to verify their identity.

a. Patients should be prepared to show identification before obtaining an opioid pain prescription. This corroboration enables a thorough evaluation of the individual's PDMP profile and adds another safeguard against "doctor shopping."[68]

16. Emergency medicine physician groups are strongly encouraged to collect and share individual opioid prescribing patterns with fellow clinicians.

a. Opioid prescribing practices vary widely among emergency physicians. Recent data suggests a striking three- to 10-fold difference in the number of opioid prescriptions written by the lowest and highest prescribing emergency physicians.[98,99] One retrospective study showed a 22-fold variation in the rate of opioids dispensed at discharge for acute low back pain, with some providers prescribing opioids for as many as 88.1% of these cases.[100]

b. Emergency physicians are advised to approach opioid prescribing with the same stewardship they employ when making other medical decisions. Tracking prescribing patterns and providing the comparative data to every clinician within the practice is recommended to combat practice deviations.

c. Emergency medicine physicians are encouraged to monitor the opioid prescribing patterns of other clinicians providing care under their license, including resident physicians and advanced practice providers. While these supervised providers do not appear to universally administer more opioids than attending physicians, oversight is recommended to decrease variability and encourage appropriate opioid prescribing practices.[101-103]

d. Information on prescribing patterns should not be used punitively; instead, it should be used to help clinicians understand their own treatment habits and facilitate change. Local sharing has been shown to significantly reduce the number of opioids prescribed at discharge.[104]

Limiting Opioid Use in the Emergency Room continued

Policy Recommendations

1. **Improve PDMPs through interoperability and automated integration into EHRs.**
   a. Although the Colorado PDMP is an important tool for preventing inappropriate opioid prescribing and misuse, it is cumbersome to use and often incompatible with busy ED 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 patterns of abuse 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.[105] Systems that incorporate such technology are overwhelmingly favored by clinicians, 98-100% of whom report improved access.[106]

2. **Pain should not be considered a "fifth vital sign," and clinical medicine should move to de-emphasize numeric rating scales and incorporate functional assessments into pain management pathways.**
   a. Long labeled as the "fifth vital sign," pain has developed enormous leverage in the American medical lexicon.
   b. While a patient's subjective discomfort is an important component 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. Medicine has overemphasized pain; as a result, physicians often feel pressured to prescribe opioids to normalize this "vital sign."
   d. While emergency physicians are trained to address pain scores reflexively, pain is a complex biopsychosocial phenomenon that cannot be distilled into a one-dimensional numerical target.
   e. Numerical pain scores can increase the risk of overtreatment and unintentional overdose in hospital settings.[107]
   f. Functional pain scales, which focus on a patient's ability to perform daily activities, are more clinically relevant than numerical scores and do not reflexively result in 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 suffer from chronic pain, while millions more experience acute pain on any given day. Pain affects more Americans than cancer, diabetes and heart disease combined, and is the most common reason Americans access the health care system. It is a leading cause of disability and a major contributor to U.S. health care costs.[108] Despite the ubiquity of pain in medical practice, the disorder is poorly understood by many medical professionals and seldom taught in medical schools, 96% of which have no dedicated pain medicine modules.[109] 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 analgesia. Appendix I, Understanding Pain: A Complex Biopsychosocial Phenomenon, provides a brief overview of how clinicians should conceptualize pain.

Using multimodal, nonopioid medications and nonpharmacological treatments to address pain is a proven strategy to mitigate patient and reduce community exposure to opioids. The vast majority of Colorado EDs have already successfully implemented such ALTO programs.[110] The following material contains pathways and recommendations that refine and update Colorado ACEP's *2017 Opioid Prescribing & Treatment Guidelines*. The ALTO program uses the CERTA (channels, enzymes, receptors targeted analgesia) framework to treat the physiologic components of pain. By intervening at multiple points in the physiologic pathways involved in pain signaling transmission, emergency physicians can leverage the complementary mechanisms of analgesia provided by different medication classes — including Cox-1, 2, 3 inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists, sodium channel blockers and GABA agonists/modulators — to treat pain more comprehensively.

ALTO programs also emphasize treating the psychological and social components of pain through nonpharmacologic interventions, pharmacological treatments (when appropriate) and education. A stepwise, additive and multimodal approach should be deployed in which opioids are used as a last resort and as adjuncts to nonpharmacologic and ALTO medications for the management of uncontrolled pain.

When selecting multimodal analgesia, emergency clinicians must contend with the lack of high-quality, diagnosis-specific evidence for many of the agents and combinations of agents available.[111] Further research is needed to determine the quality of evidence and strength of recommendation for many of the medications and pathways described below. This lack of evidence must be weighed against the incontrovertible evidence of immediate and long-term harms caused by overreliance on opioid analgesia. It is important that emergency clinicians partner with researchers, pharmacists and nurses to define and implement safe and effective analgesic protocols, taking into account the available and evolving data and integrating it in a way that is compatible with their unique practice settings.

Practice Recommendations

1. **EDs and clinicians are encouraged to apply ALTO principles when managing pain:**
   a. Use nonopioid approaches as first-line therapies.
   b. Use several agents for multimodal pain control rather than relying on monotherapies.
   c. Use opioids primarily as rescue medications.
   d. Discuss realistic, functional pain management goals with patients.
   e. Use empathic language when discussing pain.
2. **EDs are encouraged to implement ALTO programs and provide opioid-sparing pain treatment pathways for the following conditions:**
   a. Headache
   b. Abdominal pain
   c. Cyclic vomiting syndrome/cannabis hyperemesis syndrome
   d. Renal colic
   e. Musculoskeletal pain
   f. Extremity fracture/dislocation
   g. Dental pain

Alternatives to Opioids for the Treatment of Pain continued

3. **EDs are urged to integrate ALTO treatment strategies and pathways into their computerized physician order entry systems to facilitate a seamless adoption and the safe delivery of novel medications.**
4. **Emergency clinicians are advised to develop a familiarity with ALTO procedures, including regional nerve blocks, hematoma blocks, intra-articular injections and trigger-point injections for the treatment of acute pain. Emergency clinicians can work with hospitals to ensure that they are credentialed and have the tools necessary to perform ALTO procedures.**
5. **Low-dose, sub-dissociative ketamine (0.1–0.3 mg/kg) IV is an effective analgesic that can be opioid-sparing for many acute pain syndromes. It is important that the administration of sub-dissociative doses by nursing staff be supported by appropriate education and hospital policies.**
6. **Lidocaine (1.5 mg/kg) IV is an effective analgesic that can be used to treat many acute pain syndromes. The routine administration of this drug should be supported by appropriate education and hospital policies.**
7. **Antipsychotics including haloperidol, droperidol and olanzapine are safe and effective analgesics that can be used to treat many acute pain syndromes. The routine administration of the drug should be supported by appropriate education and hospital policies.**
8. **Topical medications are safe and effective for the treatment of many types of pain and are especially useful in physiologically fragile patients, including the elderly and those with liver, cardiac or renal disease. Topical medications including lidocaine, diclofenac, menthol and capsaicin should be added to ED formularies.**
9. **ED clinicians are encouraged to familiarize themselves with the principles of identifying and treating different types of pain:**
    a. For somatic or pain with an inflammatory component, consider NSAIDs, APAP, topical therapies and ALTO procedures (regional analgesia, trigger-point or joint injections).
    b. For pain with a tension or spastic component, consider muscle relaxants or antispasmodics.
    c. For pain with a neuropathic component, consider gabapentinoids or IV lidocaine.
    d. For pain associated with marked anxiety, consider low-dose antipsychotics.
    e. For chronic neuropathic, musculoskeletal or abdominal pain, consider an amine-reuptake inhibitor (e.g., duloxetine, nortriptyline, venlafaxine).
10. **Nonpharmacologic options such as distraction and comfort items, ice, heating pad, therapeutic mobility and positional adjustments can be used concomitantly with pharmacologic options for the treatment of all kinds of pain.**
11. **It is recommended that outpatient prescribing patterns follow ALTO principles by using multimodal opioid alternatives and nonpharmacologic approaches as first-line therapies. Opioids are best reserved for severe breakthrough pain when indicated.**
    a. Strongly consider the concomitant use of APAP and ibuprofen for the treatment of most painful conditions. An effective regimen is APAP 650 mg PO and ibuprofen 400 mg PO every six hours.
    b. Strongly consider the use of topical medications for pain control, including topical lidocaine, menthol, capsaicin and diclofenac.
    c. Opioids are recommended only as rescue therapies, and it is advised they be stopped as soon as pain is tolerable.
    d. Monoproducts of opioids, including oxycodone, hydromorphone and morphine sulfate, are preferred over combination products that contain APAP. This allows APAP to be taken preferentially and used as a first-line agent with less risk of supratherapeutic dosing or accidental poisoning.
    e. The concurrent receipt of opioids and nonopioid analgesic medications can reduce total opioid requirements and improve pain management.[112]
12. **As of this writing, no definitive, high-quality studies support the safety and efficacy of dispensary or pharmaceutical cannabinoids for analgesia. Until better evidence is available, physicians are discouraged from endorsing the use of cannabinoids for pain management. (See Appendix XI, Cannabinoids and Pain, for a brief review of this topic and recommendations for counseling patients.)**

ALTO Medications

The following section describes a variety of ALTO medications. Table 5 summarizes these medications and procedures.

(TABLE 5)

Summary of Multimodal Analgesic Agents and Procedures

Type	Examples
Nonopioid analgesics	APAP, NSAIDs (Cox-1, 2, 3 inhibitors)
Alpha-2 adrenergic agonists	Clonidine, dexmedetomidine
Amine reuptake inhibitors	Amitriptyline, duloxetine, nortriptyline, venlafaxine
Antipsychotics	Droperidol, haloperidol, olanzapine
Gabapentinoids	Gabapentin, pregabalin
Glucocorticoids	Dexamethasone, hydrocortisone, prednisolone, prednisone
Local anesthetics/sodium channel blockers	Bupivacaine, lidocaine, ropivacaine
Muscle relaxants/antispasmodics	Baclofen, cyclobenzaprine, dicyclomine, metaxalone, methocarbamol, tizanidine
N-methyl D-aspartate receptor antagonists	Dextromethorphan, ketamine, magnesium
Other	Capsaicin, desmopressin, menthol, nitrous oxide, oxytocin, tamsulosin
Procedures for regional or local analgesia	Compartment block Hematoma block Peripheral nerve block Trigger-point injections/dry needling

Alternatives to Opioids for the Treatment of Pain continued

APAP

EVIDENCE: APAP has been shown to significantly reduce pain compared to placebo without increased adverse events. The number needed to treat (NNT) to achieve pain relief is four.[113] Combined treatment with APAP (1000 mg) and ibuprofen (400 mg) appears to be as effective as oral opioid combinations (e.g., oxycodone or hydrocodone with APAP) for the treatment of acute extremity pain.[114]

MECHANISM OF ACTION: While not completely understood, the drug's mechanism of action is theorized to be the activation of descending serotonergic pathways. APAP increases the pain threshold by inhibiting central prostaglandin synthesis (specifically, cyclooxygenase [COX-2]).

DOSING: APAP is a readily available, inexpensive, effective option for most mild to moderate pain conditions. Doses of 400-1000 mg can be given every four to eight hours in the ED or at the time of discharge. Important: This dose should not exceed 3000 mg per 24-hour period.

OPTIONS: APAP is available in oral (PO), rectal (PR) and IV formulations; however, the IV formulation should be reserved for patients who are unable to receive medications rectally or by mouth.[116]

CONTRAINDICATIONS AND CAUTIONS: Life-threatening cases of acute hepatic failure that lead to liver transplant or death have been linked to the use of APAP. In most cases of hepatic injury, APAP doses exceeded maximum daily limits and often involved the use of more than one APAP-containing product. Hepatotoxicity has been reported with doses of 4 g or more per day; therefore, a lower maximum dose of 3 g per day in adults with normal liver function is recommended, particularly if the duration of use exceeds seven days.

HEPATIC DOSING: In patients with cirrhosis and stable liver function tests, a maximum total daily dose of 2 g is recommended.[117]

MONITORING: Check liver function tests, especially if the patient has pre-existing liver disease.

DISCHARGE INSTRUCTIONS: Instruct the patient to avoid other over-the-counter products that contain APAP and limit the total daily dose to less than 3000 mg.

AMINE REUPTAKE INHIBITORS

EVIDENCE: Although chronic pain and depression are often comorbid conditions, amine reuptake inhibitors are thought to produce an antihyperalgesic effect (independent of their mood-stabilizing ability) by suppressing the noradrenergic descending inhibitory system.[115] Antidepressants have been widely used off-label for the treatment of chronic pain. In particular, venlafaxine (an SNRI) and nortriptyline (a tricyclic antidepressant [TCA]) should be strongly considered for the first-line treatment of neuropathic pain.[118] Duloxetine (an SNRI) should also be considered, as it is noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy.[119] Duloxetine and TCAs may reduce abdominal pain and increase quality of life in patients with irritable bowel syndrome.[120] Duloxetine should be considered as an adjunct therapy for patients with chronic neuropathic, musculoskeletal or abdominal pain who are receiving other first-line treatments.

MECHANISM OF ACTION: Influence on affective components of pain. TCAs and SNRIs increase the concentration of norepinephrine in the spinal cord, a process that inhibits neuropathic pain through α2-adrenergic receptors.

OPTIONS: SNRIs (e.g., duloxetine, venlafaxine) and TCAs (e.g., amitriptyline, nortriptyline)

DOSING: Dosing should be based on effect and tolerability.

- Duloxetine: Start at 30 mg PO daily, then increase to 60 mg PO daily after one week.
- Venlafaxine: Start at 75 mg PO daily, then increase by 75 mg every four days to 150-225 mg PO daily.
- Amitriptyline: Start with 10 mg PO at bedtime; may titrate up to 50 mg PO at bedtime.
- Nortriptyline: 12.5 mg PO once daily at bedtime; may increase as tolerated up to 35 mg/day. Best used for chronic pain. Do not stop abruptly. May take one week or longer to take effect.

CONTRAINDICATIONS AND CAUTIONS: SNRIs and TCAs may increase the risk of suicide in patients aged 18 to 25 years. Avoid TCAs in the elderly (Beers criteria) due to anticholinergic effects.

MONITORING: Patients taking SNRIs should be monitored for serotonin syndrome. Monitor the QT interval (at baseline and periodically) of patients taking TCAs.

DISCHARGE INSTRUCTIONS: Close follow-up with an outpatient primary care provider is essential to ensure appropriate titration to target doses. These medications require time to reach an effective dose and an adequate duration should be trialed before concluding treatment failure. Provider oversight is also important to monitor for adverse effects and initiate the safe discontinuation of therapy if deemed necessary.

Antipsychotics

HALOPERIDOL

EVIDENCE: Haloperidol is a first-generation antipsychotic agent that is often used for psychiatric emergencies. It has analgesic and antiemetic properties and has been shown to be an effective treatment for cyclic vomiting and cannabis hyperemesis syndrome, both of which can be very difficult to treat.[121,122] It is recommended that Haloperidol be considered a first-line treatment option as part of an opioid-sparing pathway for these conditions. At doses of 2.5-5 mg, the drug is effective for the management of abdominal pain and migraine-associated headaches.[123,124] It has been shown to reduce pain intensity and nausea scores in patients with suspected gastroparesis.[125]

MECHANISM OF ACTION: Nonselective blockade of postsynaptic dopaminergic D2 receptors. Its mechanism of action for pain reduction is not completely understood. Antiemetic effects are thought to be due to blockade of these receptors in the chemoreceptor trigger zone. It also has weak anticholinergic effects.

DOSING: 2.5-5 mg IV/intramuscular (IM)/PO.

Options: It can be administered intravenously, intramuscularly or orally.

CONTRAINDICATIONS AND CAUTIONS: There is a higher risk of QT-interval prolongation and torsade de pointes when administered via IV 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 electrocardiogram (ECG) and repeat periodically during therapy.

DROPERIDOL

EVIDENCE: Droperidol is a first-generation antipsychotic agent that has been used in the ED for the treatment of migraines, nausea and vomiting and acute agitation. In 2001, the U.S. Food and Drug Administration (FDA) issued a black box warning related to concerns of QT-interval prolongation and increased risk of torsades de pointes. Droperidol has since been removed from many hospital formularies; however, these concerns have been called into question based on the lack of significant adverse outcomes in ED populations.[126] Commentary has further questioned the necessity of the black box warning. In 2013, the American Academy of Emergency Medicine issued a clinical practice statement supporting the use of droperidol 2.5 mg IV or IM doses or less without the need for ECG or telemetry monitoring.[127] A systematic review of droperidol for the management of acute headaches and migraine showed the drug improved pain relief when compared to placebo, prochlorperazine and meperidine.[128] One randomized controlled trial comparing droperidol to metoclopramide and prochlorperazine for the treatment of nausea and vomiting found that droperidol 1.25 mg IV was significantly better at nausea reduction than the other medications.[129]

MECHANISM OF ACTION: Several mechanisms are theorized to contribute to the analgesic effects of droperidol. Most notably, droperidol blocks postsynaptic dopaminergic D2 receptors, which is thought to augment the response to opioids and aid with nausea. It also exhibits GABA-agonistic effects, which may inhibit pain transmission. Additionally, it appears to enhance u-receptor expression and binding in the spinal cord.

DOSING: Droperidol 0.625–2.5 mg IV/IM.

OPTIONS: It can be administered intravenously or intramuscularly.

CONTRAINDICATIONS AND CAUTIONS: Doses of 2.5 mg or less have not been associated with significant adverse effects; cardiac monitoring is not necessary. However, caution is advised if treating patients with known QT-prolongation or underlying cardiac abnormalities, if using multiple concomitant QT-prolonging drugs, or if the total dose exceeds 2.5 mg.

MONITORING: If no significant risk factors are present and the patient is receiving a dose of 2.5 mg or less, a baseline ECG and telemetry monitoring are not required.

OLANZAPINE

EVIDENCE: While a first-line treatment for schizophrenia, there is growing evidence to support the antiemetic properties of olanzapine, particularly in chemotherapy patients.[130] The analgesic properties of olanzapine have also been noted in randomized control trials focused on the treatment of migraine headaches and fibromyalgia.[131,132] Based on expert opinion and clinical experience, olanzapine is recommended for the management of cyclic vomiting syndromes (particularly cannabis hyperemesis), for which it appears to offer both analgesic and antiemetic benefits.[133] The drug may be an effective agent for the treatment of other painful conditions, including headaches and fibromyalgia.

Alternatives to Opioids for the Treatment of Pain continued

MECHANISM OF ACTION: Olanzapine is a second generation atypical antipsychotic with high affinity for serotonin and dopamine receptors, as well as antagonist activity at muscarinic receptors. However, its exact mechanism of action for antipsychotic effects is still relatively unknown.[134]
DOSING: Recommended initial dose is 5 mg IV/IM/sub-lingual (SL)/PO. At discharge, a 5 mg orally disintegrating tablet (ODT) is recommended every six to eight hours as needed for nausea, vomiting or abdominal pain.
OPTIONS: Olanzapine can be given intramuscularly, intravenously, orally and sublingually as an orally disintegrating tablet.
CONTRAINDICATIONS AND CAUTIONS: Somnolence, orthostatic hypotension and cardiac conduction abnormalities have been reported with olanzapine use. Caution should be exercised when using IV administration, when prescribing high doses and in patient populations known to metabolize olanzapine more slowly (e.g., nonsmokers, women, elderly).

CAPSAICIN

EVIDENCE: Capsaicin is the derived active ingredient in chili peppers and is a natural analgesic produced in topical applications including creams, ointments and patches. It acts on nociceptive pain fibers by desensitization, thus inhibiting pain transmission.[135] Topical capsaicin has shown benefit in multiple applications including rheumatoid arthritis, osteoarthritis and post-herpetic neuralgia.[136] While evidence is of lesser quality, research and experience is mounting for capsaicin being an effective treatment of pain associated with cannabis hyperemesis syndrome (CHS).[137-139] Capsaicin can easily be prescribed for home and is available over the counter. Additionally, capsaicin is considered Category B for pregnancy risk factor with no observed adverse events in animal reproduction studies, which may allow more widespread administration as well as prior to pregnancy test results.
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.
DOSING: Creams and ointments are likely to be the most convenient and are available in concentrations ranging from 0.025% to 0.1%. Capsaicin 0.1% cream apply a thin layer to affected area four times daily as needed for pain. For CHS, apply a thin layer over the abdomen.
CONTRAINDICATIONS AND CAUTIONS: May cause burning, redness or pain at the site of application. It has a very good safety profile, particularly when compared to other agents used for these common conditions.
DURATION OF USE: Burning should reduce with repeated administration. May take one to four weeks for maximal pain relief.

DEXAMETHASONE

EVIDENCE: Glucocorticoids, and predominantly dexamethasone, have been shown to be efficacious in the treatment of acute migraine headache, dental pain and sore throat and may be an effective adjunct to other anti-inflammatories. Added to a typical headache regimen, dexamethasone has been shown to reduce headache recurrence at 24 and 72 hours in one meta-anaylsis.[140] When given for postoperative dental pain, a single dose of dexamethasone has been shown to reduce pain up to seven days postoperatively.[141] When combined with gabapentin, increased dexamethasone led to improved analgesia after knee arthroplasty, suggesting a possible role in post-procedural pain control.[142]
MECHANISM OF ACTION: Glucocorticoids (e.g., dexamethasone and methylprednisolone) have many actions including analgesic, antiemetic, antipyretic and anti-inflammatory effects. Although not completely clear, analgesic effects of dexamethasone are thought to result from the inhibition of phospholipase, leading to a decrease in cyclooxygenase and lipoxygenase production.
Dosing: Dexamethasone 8-10 mg IV/IM/PO as a single dose. Repeat dosing is rarely required.
CONTRAINDICATIONS AND CAUTIONS: Long-term or repetitive use may increase risk of adverse events. Caution in patients at risk for gastric irritation. May lead to transient rise in blood glucose and require more frequent monitoring in diabetics. Repetitive or long-term use may increase risk of adrenal suppression, poor wound healing, immunosuppression, myopathy and psychiatric disturbances.

Alternatives to Opioids for the Treatment of Pain continued

DESMOPRESSIN (DDAVP)

EVIDENCE: Desmopressin provides comparable pain relief in renal colic to opioids and even more pain relief when added to opioids. No added benefit to NSAIDs.[143]
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: Contraindications include history of or current hyponatremia, polydipsia and 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 one in 10,000 patients.[143] IV route can be associated with higher risk of thrombo-embolic events.
MONITORING: Check serum sodium prior to initiation. Recheck within one week or sooner if risk for hyponatremia.

DICYCLOMINE

EVIDENCE: It is effective for treating abdominal pain, particularly caused by cramping, and has been shown to be beneficial in irritable bowel syndrome.[144-147]
MECHANISM OF ACTION: Antispasmodic and anticholinergic effects that alleviate smooth muscle spasm of the GI tract.
DOSING: Dicyclomine 10-20 mg IM/PO every six hours as needed for abdominal cramping.
OPTIONS: Dicyclomine can be administered either orally or intramuscularly. It should NOT be administered intravenously due to risk of thrombosis and thrombophlebitis.
CONTRAINDICATIONS AND CAUTIONS: Dicyclomine can be an effective pain reliever in pregnant patients as a Category B drug. Avoid use in elderly patients due to anticholinergic effects (Beers criteria) or patients at increased risk for delirium.[148] May worsen urinary retention or ileus.

GABAPENTIN AND PREGABALIN

EVIDENCE: Four out of 10 patients with neuropathy will achieve 50% pain relief with gabapentin.[149] Pregabalin has better oral bioavailability and faster onset of action (one hour versus three hours with gabapentin). Pregabalin alone or combined with ibuprofen has shown efficacy with postoperative pain after third molar extraction.[150,151]
MECHANISM OF ACTION: Inhibits alpha 2-delta subunit of voltage-gated calcium channels, believed to decrease conduction of neuropathic pain sensation.
DOSING: Gabapentin 300-600 mg or pregabalin 75-150 mg. If prescribed at discharge, initiate with low doses and titrate to effective dose based on tolerability. Gabapentin: start at 100-300 mg PO three times daily, then increase by 100-300 mg per day every one to seven days as tolerated up to 1200 mg three times daily. Pregabalin: start at 75 mg PO twice daily, then increase by 150 mg per day every three to seven days as tolerated up to 300 mg PO twice daily.
RENAL DOSING: Adjust dose for renal impairment.
CONTRAINDICATIONS AND CAUTIONS: Avoid use in older adults with a history of falls as it may cause syncope, impaired psychomotor function or ataxia. Caution is advised in patients taking concomitant opioids or CNS depressants with underlying respiratory diseases such as COPD and in elderly patients due to risk of increased respiratory depression. Avoid abrupt discontinuation.
MONITORING: Consider checking serum creatinine.
Discharge: Gabapentinoids have potential for misuse and abuse. Pregabalin is a Schedule V controlled substance. Although it has the lowest potential for abuse relative to other controlled substances, it does require the prescribing provider to have an active DEA number.

Local Anesthetics (LA)

INTRAVENOUS:

EVIDENCE: Intravenous lidocaine is safe for neuropathic pain, better than placebo and as effective as other analgesics.[152] An intravenous lidocaine infusion has shown to provide effective analgesia associated with postoperative pain, headaches and neurologic malignancies.[153,154] Also shown to improve pain in renal colic and critical limb ischemia compared to morphine in the ED.[155,156] Analgesia in renal colic is increased when combined with ketorolac.[115]

MECHANISM OF ACTION: Blocks conduction of nerve impulses through inhibition of sodium channels.

DOSING: Lidocaine 1.5 mg/kg IV in 100 mL normal saline (NS) over 10 minutes (max 200 mg).

CONTRAINDICATIONS: Avoid in unstable coronary disease, recent myocardial infarction (MI), heart failure, severe electrolyte disturbances, cirrhosis, arrhythmia, seizure disorders.

CAUTIONS: Local anesthetic systemic toxicity (LAST) 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 uses IV lidocaine.

REGIONAL ANESTHESIA/LOCAL INJECTION:

EVIDENCE: Administration of LAs via subcutaneous infiltration is ideal for minor localized injuries or procedures such as open wound repair, abscess drainage and foreign body removal. Local anesthetics also appear to have potential analgesic properties for both the treatment of acute and chronic pain when administered by intra-articular injection. Evidence suggests intra-articular lidocaine provides a similar success rate for shoulder reductions compared to intravenous sedation.[158] However, intra-articular lidocaine also appears to have fewer complications, shorter length of stay and lower cost compared to intravenous sedation.[159,160] Even for the treatment of chronic knee pain, such as that from osteoarthritis, local anesthetics may have potential for pain relief. A double-blind, randomized controlled trial (RCT) demonstrated reduction in pain at three months after three weekly intra-articular injections of 0.5% lidocaine in those with osteoarthritis.[161] Use of local anesthetics in regional nerve blocks by emergency physicians has demonstrated efficacy in the reduction of opioid consumption, particularly in elderly patients and hip fractures.[162]

MECHANISM OF ACTION: Blocks conduction of nerve impulses through inhibition of sodium channels.

Options: Bupivacaine and ropivacaine are common alternative LAs that may be preferred due to their higher potency and longer duration of action. LAs may also be administered via direct infiltration into a targeted nerve plexus. This technique has been successfully used for orthopedic injuries such as femur and hip fractures by performing a fascia iliaca block via ultrasound guidance or with an anatomic approach. For prolonged analgesic effect, placement of a catheter connected to an elastomeric pump can provide continuous peripheral nerve blockage for up to five days and has been successfully used as the primary analgesic for patients with rib fractures.

CAUTIONS: Side effects of these drugs are minimal when used sparingly or in low doses, however providers should be familiar with signs and symptoms of LAST and appropriate treatment with intralipid therapy. The risk of LAST may increase with regional anesthesia and can be partially reduced based on expert opinion with the use of ultrasound guidance.

Alternatives to Opioids for the Treatment of Pain continued

TOPICAL:

EVIDENCE: Lidocaine is effective in a transdermal (4% or 5%) patch that may be used on intact skin for controlling neuropathic pain, post-herpetic pain, musculoskeletal injuries and low back pain.[163,164] Other formulations of lidocaine, including ointment and creams, may be effective during painful procedures such as wound debridement, or for minor acute injuries involving broken skin such as road rash, abrasions and burns.[165]

MECHANISM OF ACTION: Blocks conduction of nerve impulses through inhibition of sodium channels.

DOSING: Lidocaine 4% or 5% transdermal patch to affected area of intact skin every 24 hours.[166] Up to three patches may be applied in a single application. Lidocaine 5% cream apply to affected area up to six times daily. Lidocaine 5% ointment apply up to 5 g to affected area four times daily.

Contraindications and Cautions: Transdermal patches are only recommended to use on intact skin. Creams or ointments may be used on minor injuries of broken skin. Total lidocaine doses should not exceed 4.5 mg/kg or 300 mg.

DISCHARGE: If 5% prescription concentration is cost prohibitive, can prescribe lidocaine 4%, which is over-the-counter.

MENTHOL TOPICAL

EVIDENCE: Methyl salicylate and menthol provide significant pain relief of muscle strain compared to placebo.[167] In a small study, menthol was more effective than ice.[168]

MECHANISM OF ACTION: Stimulates receptors producing cold sensation.

CONTRAINDICATIONS AND CAUTIONS: Recommend use only on intact skin.

MUSCLE RELAXANTS/ANTISPASMODICS

EVIDENCE: Cyclobenzaprine reduces low back pain with an NNT of three.[169] It can also reduce pain scores in patients with renal colic who are receiving NSAIDs, though the difference was not statistically significant.[170]

MECHANISM OF ACTION: Cyclobenzaprine: acts in the brainstem and reduces tonic somatic motor activity; structurally similar to TCAs. Tizanidine: alpha-adrenergic agonist. Methocarbamol and metaxalone: depress 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 a low dose and increase to effect while monitoring sedation. Cyclobenzaprine 5-10 mg PO one to three times daily. Tizanidine 2-4 mg PO once or twice daily. Methocarbamol 800 mg PO three or four times daily. Baclofen 5-10 mg PO three times daily.

CONTRAINDICATIONS AND CAUTIONS: Avoid use in elderly patients (Beer's criteria) or patients at increased risk for delirium. All antispasmodics may cause sedation, but anecdotally less sedation is seen with methocarbamol. For tizanidine, may cause bradycardia, hypotension.

DURATION OF USE: Use for shortest possible duration due to sedative side effects. Do not abruptly discontinue baclofen.

N-methyl D-aspartate Receptor Antagonists

KETAMINE

EVIDENCE: Ketamine has been used extensively in the ED for procedural sedation and rapid-sequence intubation. Recent research has demonstrated that a low (sub-dissociative) dose is safe and effective for pain management.[171-173] Low-dose, sub-dissociative ketamine (0.1-0.3 mg/kg) is an effective analgesic that can be opioid-sparing for many acute pain syndromes and should be added to ED formularies.

MECHANISM OF ACTION: Antagonizes NDMA receptors in the CNS.

DOSING: Low-dose initial bolus of 0.1-0.3 mg/kg IV, best tolerated if given as an infusion over 10-15 minutes. Due to the relatively short-lived analgesic effects of ketamine, the initial bolus can be followed by an infusion of 0.1 mg/kg/hour for sustained effect.[174] Ketamine may also be administered as a 0.5 mg/kg (max 50 mg) IN dose in those patients without an IV.

CONTRAINDICATIONS AND CAUTIONS: Caution should be used if the patient has a history of 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 syndrome. Ketamine can cause dose-dependent sedation. Feelings of unreality and sedation have been associated with low-dose ketamine when given as an intravenous push. These effects may be mitigated if dose is delivered as a slow infusion over 15 minutes,[175] or may be counteracted by administering a low-dose benzodiazepine.

ADVERSE EFFECTS: Hypertension, tachycardia, myocardial depression, increased intracranial pressure, vivid dreams, anxiety, hallucinations, tremors, tonic-clonic movements, nausea, sedation.

MONITORING: Vitals should be checked immediately after IV dose given and every 15 minutes thereafter for at least one hour. If acute change in vitals or intolerable psycho-mimetic effects, stop ketamine and consider benzodiazepine for psycho-mimetic effects.

DISCHARGE: Ketamine should not be routinely prescribed at discharge. Ketamine is a Schedule III drug with potential for abuse.

MAGNESIUM

EVIDENCE: In a double-blind controlled study, intravenous magnesium sulfate was associated with significant improvement in migraine pain and associated symptoms, particularly in migraines associated with aura.[176] A recent systematic review of IV magnesium for acute, non-traumatic headaches treated in the ED concluded that the existing evidence indicates potential benefits in pain control beyond one hour, aura duration and the need for rescue analgesia.[177] Studies in the anesthesiology literature also report improvement in analgesia and reduction in opioid requirements when magnesium is used as an adjunct in surgical patients.[178-180]

MECHANISM OF ACTION: Blockade of NMDA receptor and modulation of many intracellular signaling cascades is thought to play a role in the analgesic effects of magnesium. Through regulation of serotonin release, magnesium allows blood vessel dilation. Magnesium also modulates the release of leukotrienes, prostaglandins and the neuropeptide substance P, which may also influence pain sensitivity.

DOSING: Magnesium 1-2 g IV over 20 minutes. Magnesium has a relatively large therapeutic index, with concerns of accumulation mostly in the renally impaired population.

CONTRAINDICATIONS: Avoid in patients with heart block. Use caution in patients with renal impairment.

MONITORING: Cardiovascular monitoring is recommended due to the risk of hypotension.

SPECIAL CONSIDERATIONS: If transitioning to oral therapy for outpatient management, need to consider significant gastrointestinal side effects (e.g., diarrhea).

Alternatives to Opioids for the Treatment of Pain continued

NITROUS OXIDE

Evidence: Featuring a rapid-onset and elimination (<60 sec), nitrous oxide exhibits both analgesic and anxiolytic properties. There is evidence to support its role in the management of pediatric pain and sedation, pre-hospital pain relief and during colonoscopic and bronchoscopic procedures.[181-184] Additional indications for the use of nitrous oxide include laceration repair, incision and drainage, wound care, foreign body removal, central venous access, peripheral venous access, fecal disimpaction and as an adjunct for dislocations and splinting.

MECHANISM OF ACTION: Nitrous oxide is a tasteless, colorless gas administered in combination with oxygen via a mask or nasal hood at a maximum concentration of 70%. The gas is absorbed via pulmonary vasculature and does not combine with hemoglobin or other body tissues.

OPTIONS: There are no nil per os (NPO) requirements – patients can drive after administration and no IV line is needed.

MONITORING: Pulse oximetry is the only patient monitoring required.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

EVIDENCE: When combined with APAP, NSAIDs can reduce acute pain by 50% in seven out of 10 patients.[185] Adding an NSAID to a pain regimen containing an opioid may have an opioid-sparing effect of 20% to 35%.[186] For renal colic, both opioids and NSAIDs lead to a clinically relevant reduction in pain scores; however, opioids are associated with higher rates of adverse reactions, particularly vomiting.[187]

MECHANISM OF ACTION: Inhibits proinflammatory prostaglandin production via the inhibition of COX-1 and COX-2 enzymes.

DOSING: Ketorolac 10 mg IV or 15 mg IM; may be given up to every six hours. Ibuprofen 400 mg PO every six hours.

OPTIONS: Ibuprofen, naproxen, ketorolac, diclofenac, indomethacin and selective COX-2 inhibitors (e.g., meloxicam, celecoxib). While ibuprofen is generally used throughout these guidelines as the oral agent of choice, providers may use clinical and practical discretion on when to substitute a different NSAID option.

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. Conversely, nonselective NSAIDs pose a lower risk of cardiac side effects but a higher risk of GI side effects.

CONTRAINDICATIONS AND CAUTIONS: NSAIDs increase the risk of MI and stroke. Contraindicated in the setting recent coronary artery bypass graft surgery or MI. 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 (Beer's 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: Special caution should be used in patients with renal dysfunction, heart failure and concern for bleeding.[188] For these subpopulations, consider using topical choices such as diclofenac gel or patch. Topical options have significantly lower systemic absorption and lower rates of adverse drug events.

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.

Alternatives to Opioids for the Treatment of Pain continued

(TABLE 6)

Risk of Gastric Ulcer Bleeding with NSAIDs[189]

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)

(TABLE 7)

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[190,191]

TOPICAL NSAIDS

EVIDENCE: To achieve a 50% reduction in musculoskeletal pain, NNT was 3.7 for topical diclofenac topic solutions, which is about the same for oral NSAIDs.[192] Only about 5% of topical NSAIDs are systemically absorbed compared to oral NSAIDs but studies show there is local absorption into tissues and synovium. 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 1% gel, 1.3% patch and 1.5-2% 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.[193]
DISCHARGE: More expensive than oral NSAIDs.

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.[194]
MECHANISM OF ACTION: Alpha-1 receptor antagonist, produces smooth muscle relaxation.
DOSING: Tamsulosin 0.4 mg PO daily until stone passage.
CONTRAINDICATIONS AND CAUTIONS: May cause orthostatic hypotension, complications with cataract surgery and abnormal ejaculation.
DURATION OF USE: Until stone passage.

Novel Agents

The following agents may warrant further investigation for use in the practice of emergency medicine, given their utilization as analgesics in other specialties.

ALPHA-2 AGONISTS (CLONIDINE, DEXMEDETOMIDINE)

EVIDENCE: Studies have demonstrated that clonidine and dexmedetomidine elicit opioid-sparing effects, improve pain control and minimize opioid-related side effects, most notably when used in the inpatient, perioperative setting.[195,196] When used in outpatient dental procedures, intranasal dexmedetomidine produced greater intra- and postoperative analgesia compared to ketamine and midazolam.[197] In conjunction with regional anesthetics, both agents increase the anesthetic duration of effect and prolong analgesia.[198-201] Dexmedetomidine, when combined with ketamine, has also demonstrated the ability to enhance analgesic effects while reducing the incidence of ketamine-related adverse effects such as emergence reactions and nausea and vomiting.[202,203] Alpha-2 agonists also help to control pain and alleviate opioid withdrawal symptoms in difficult-to-manage pain in patients receiving MAT or chronic opioid therapy. While there have not been any large-scale clinical trials conducted, the current body of evidence suggests that dexmedetomidine and clonidine are suitable for ED patients as adjunct analgesics, in particular for preprocedural use, in conjunction with regional anesthetics or for patients who are on chronic opioid therapy or MAT who have uncontrolled pain.

MECHANISM OF ACTION: Relatively selective alpha-2 adrenergic agonist with anesthetic and sedative properties thought to be due to inhibition of norepinephrine release.

DOSING: Dexmedetomidine 0.2-1.5 mcg/kg/hr continuous infusion, based on level of sedation and side effects. A loading infusion of 1 mcg/kg over 10 minutes may be considered but is typically avoided due to risk of bradycardia; Dexmedetomidine 1 mcg/kg IN. Clonidine 0.1-0.2 mg per dose PO two to four times daily; must be tapered when discontinued to avoid rebound hypertension.

CONTRAINDICATIONS AND CAUTIONS: Use caution in patients with advanced heart block or severe ventricular dysfunction. Bradycardia and hypotension may be more pronounced in the elderly and patients with hypovolemia – dosage reduction is recommended.

MONITORING: Potential adverse effects, such as hypotension and bradycardia, must be taken into consideration by clinicians. While a dexmedetomidine infusion may be continued postoperatively, regardless of extubation status, most hospital policies will require patients on an infusion to be monitored in an intensive care setting.

DEXTROMETHORPHAN

EVIDENCE: In a randomized, double-blind crossover trial, a single dose of dextromethorphan 270 mg PO for neuropathic pain demonstrated a 30% reduction in pain scores without any severe adverse effects compared to placebo.[204] A Canadian review found that dextromethorphan attenuated the sensation of acute pain at doses of 30-90 mg PO, without major side effects, and reduced the amount of analgesics in 73% of the postoperative dextromethorphan-treated patients.[205] A recent multicenter, randomized control trial concluded that oral dextromethorphan 30-90 mg/day regimens initiated after a ketamine infusion prolonged pain relief for over one month in patients with diabetic neuropathy.[206] Dextromethorphan is reasonable to consider for use in patients with neuropathic pain inadequately controlled using other ALTO approaches, or in patients that experience significant relief from ketamine IV that may benefit from continuation of an oral NMDA receptor antagonist.

MECHANISM OF ACTION: NMDA receptor antagonist binds to receptor sites in the spinal cord and CNS, thereby blocking the generation of central acute and chronic pain sensations arising from peripheral nociceptive stimuli and enabling reduction in the amount of analgesics required for pain control. Genetic polymorphism may play a role in the variability factor of dextromethorphan. Patients who are poor metabolizers of CYP2D6 may not be able to metabolize the parent drug to the main active metabolite, dextrorphan, which is thought to contribute significantly to the analgesic effect.

DOSING: 30-90 mg PO administered 30-90 minutes prior to surgery. Doses have also been continued as 40 mg PO three times daily for up to two days.

CONTRAINDICATIONS AND CAUTIONS: Should be avoided in patients on concurrent or within 14 days of monoamine oxidase inhibitors use.

MONITORING: May cause dizziness or somnolence. Due to single preoperative dose, additional monitoring not recommended.

METHYLXANTHINES (AMINOPHYLLINE, THEOPHYLLINE, CAFFEINE)

EVIDENCE: A dose of aminophylline 250 mg IV was found to be effective in all patients experiencing a postdural puncture headache (PDPH), with relief as soon as 30 minutes following the dose and for up to two days.[207] While theophylline lacks evidence for PDPH, it is a reasonable oral option as it is the main agent that aminophylline is converted to when administered. Caffeine, both oral and IV, have been found to be effective as well in the treatment of PDPH and are thought to work similarly as aminophylline and theophylline.[208,209] Of note, IV caffeine has been unavailable for several years and is not anticipated to return to the market. It is reasonable to consider either oral caffeine or theophylline in the management of PDPH and to use IV aminophylline in those patients unable to tolerate oral therapy.

MECHANISM OF ACTION: While the methylxanthines are known to be phosphodiesterase enzyme inhibitors, the exact mechanism by which they exert their analgesic effect is unknown. It is thought to be due to the result of CNS stimulation.

DOSING: Caffeine 300-500 mg PO as a single dose; dose may be repeated after four hours if no relief. Theophylline 250-300 mg PO, which can be given every eight hours until headache resolution. Aminophylline 250 mg IV over 20 min x one dose.

CONTRAINDICATIONS AND CAUTIONS: Use these agents with caution in patients with cardiac arrhythmias, as may exacerbate. Use with caution in patients with a known seizure disorder. Due to the short nature of duration, toxicity of theophylline (with both aminophylline and theophylline administration) is of low concern.

MONITORING: Levels of any agent is not recommended for this indication. Tachycardia and tachypnea, jitteriness and tremors may occur with administration.

OXYTOCIN

EVIDENCE: One meta-analysis, which evaluated seven studies of exogenously administered oxytocin, overall reported that exogenous oxytocin is reliably associated with decreases in pain sensitivity.[210] However, the administration and dose of oxytocin (along with the target patient populations) varied widely among studies, including intrathecal, intravenous, intranasal, inhalation and intraventricular administration of oxytocin. In a small study of patients undergoing laparoscopic surgery, a local infiltration of subcutaneous oxytocin at the surgical site was found to reduce postoperative pain in a comparable manner to infiltration of lidocaine.[211] While the association of oxytocin and pain modulation has been well-defined in animal data, there is limited (but encouraging) human research.[212] Before a formal recommendation can be made on the routine use of oxytocin in the perioperative period, there is a need for methodologically rigorous work in humans. It is reasonable to consider use of oxytocin in patients with inadequate pain control using other ALTO approaches.

MECHANISM OF ACTION: Produced in the hypothalamus, oxytocin is released into the peripheral circulation via the posterior pituitary, as well as into the CNS, including spinal fluid. At times of stress or pain, surges of oxytocin are released into the peripheral nervous system as well. In addition to activating its own receptors and decreasing pain signals, oxytocin binds to opioid receptors and stimulates endogenous opioid release in the brain.[213,214] Oxytocin also stimulates cannabinoid receptors and is known to relieve pain, reduce anxiety, induce a feeling of calm and lower serum cortisol.[214]

DOSING: Although the human studies vary widely in dose and route of administration, it seems reasonable to administer oxytocin 20-80 international units (IU) SL or oxytocin 40 IU nasal following surgery in those patients with inadequate pain control using other multimodal analgesic approaches.

CONTRAINDICATIONS AND CAUTIONS: Oxytocin is, overall, a very safe medication with few adverse effects and no contraindications outside the peripartum population.

SPECIAL CONSIDERATIONS: Do not use in pregnant patients.

Alternatives to Opioids for the Treatment of Pain continued

ALTO Procedures

A robust ALTO program relies on emergency physicians having competency in several procedures that are well within the defined scope of practice, including peripheral nerve blocks, compartment blocks, hematoma blocks, intra-articular injections and trigger point injections. These procedures allow directed analgesia, typically with local anesthetics, to be achieved with equipment readily available in most EDs. Outlined below are basic, fundamental approaches and recommendations for procedures that can be considered as part of any ED ALTO program:

REGIONAL ANESTHESIA

Regional nerve blocks provide an effective way to achieve excellent analgesia and reduce the reliance on opioids for pain control. Depending on the location of the nerve block, anesthesia can be achieved over a large area. Blocks can be performed to help facilitate pain control with acute injuries as well as aid in fracture and dislocation reduction. Simple nerve blocks may be familiar to the emergency physician and easily performed by landmark techniques (i.e., dental blocks, wrist blocks). However, more technically challenging regional anesthesia and plane blocks have increased success and safety when using ultrasound guidance. Emergency physicians are encouraged to develop competency with as many techniques as possible in order to provide opioid-free analgesic options.

EVIDENCE: Ultrasound-guided nerve blocks for intracapsular and extracapsular hip fractures,[215] ultrasound-guided infraclavicular brachial plexus blocks,[216] suprascapular nerve blocks[217] and forearm nerve blocks in pediatric patients[218] have all been shown to be effective in providing adequate pre-procedural pain relief in ED settings. These can provide a viable alternative to opioids for procedural pain management and may also be considered as a means of primary pain control and an alternative to procedural sedation for many patients.

The potential applications for regional anesthesia are extensive and continuing to grow. Below is a list of potential regional nerve blocks to consider:

- Anterior tibial nerve block
- Axillary brachial plexus nerve block - upper extremity injury,[226] deltoid abscess[227]
- Dental blocks (see pathway on dental pain for more specific information)
- Dorsal penile block – priapism, penile injury, foreign body removal[237,238]
- Erector spinae plane block – appendicitis,[241] renal colic,[242] rib fractures,[243,244] transverse process fractures[245]
- Fascia iliaca block/fascia iliaca compartment block – femoral neck fractures[247]
- Femoral nerve block
- Greater auricular nerve block
- Infraclavicular brachial plexus nerve block – elbow dislocation,[223,224] upper extremity injuries[224]
- Intercostal nerve block – thoracentesis,[232] rib fractures[233]
- Interscalene brachial plexus nerve block – shoulder dislocation reduction[221]
- Interscalene nerve block
- Median nerve block
- Popliteal sciatic nerve block – calf abscesses, ankle injuries,[228] foot injuries[229]
- Posterior tibial nerve block – calcaneal fracture,[230] foot lacerations, foreign body removal[231]
- Radial nerve block
- Serratus anterior plane block – chest procedures/ injuries,[234] rib fractures[235,236]
- Superficial cervical plexus nerve block – rotator cuff disorders, radicular pain, para-cervical muscle spasm, clavicle fracture[219,220]
- Supraclavicular brachial plexus nerve block – upper extremity injuries[222]
- Supracondylar radial nerve block
- Suprascapular nerve block – shoulder reduction[246]
- Sural nerve block
- Transverse abdominis plane block – appendicitis,[239] abdominal wall procedures[240]
- Ulnar nerve block

Emergency physicians should ensure that regional anesthetic techniques are included in the emergency medicine delineation of privileges at their facilities.

TECHNIQUE: Descriptions of each technique are beyond the scope of these guidelines. Many online resources can be found for education on nerve blocks. The following are reputable sites that may serve as a reference for emergency clinicians:

- https://www.nysora.com/
- https://cha.com/clinician-training-materials/
- http://highlandultrasound.com
- https://painandpsa.org/rnb/
  a. Equipment to facilitate safe nerve blocks including ultrasound-guided nerve blocks may not be standard and should be made available in the ED.[248]
  b. https://www.acepnow.com/article/how-to-implement-ultrasound-guided-nerve-blocks-in-your-ed/

CAUTIONS: For large administrations of local anesthetics, LAST is a potential life-threatening adverse event. EDs should strongly consider stocking intralipid in the ED and implementing protocols for LAST.

Emergency physicians are encouraged to collaborate with subspecialty services such as anesthesia, orthopedics and trauma surgery to develop patient care protocols (e.g., fascia iliaca compartment block in the geriatric hip fracture population) to help facilitate the application of regional anesthesia in the ED.

Emergency physicians should assure that they have adequate training and proficiency before performing regional anesthesia. This includes a robust understanding of the relevant anatomy, proper anesthetics, technique, monitoring and relevant documentations. Those performing such procedures should also have a thorough understanding of contraindications and potential complications including local anesthetic systemic toxicity.

JOINT INJECTIONS

Arthrocentesis is a procedure that should be very familiar to any emergency physician. Intra-articular injections recommended for use with ALTOs employ local anesthetics directly injected into the joint capsule under sterile procedures. Common joints injected may include the glenohumeral joint, knee, elbow, ankle and wrist.

EVIDENCE: The administration of local anesthetic into the joint capsule has been shown to be an excellent adjunct when performing dislocation reduction, helping reduce the reliance on both opioid administration and procedural sedation.[249,250] There is limited evidence to suggest that intra-articular blocks may provide superior analgesia to even regional nerve blocks.[251] For arthritis presentations, the administration of local anesthetic into the affected joint may be considered as an adjunct to additional medications or as an alternative when others are contraindicated.[252]

Currently, there is evidence to suggest that local anesthetics delivered through continuous infusions into the joint capsule, typically used in arthroscopic surgery, carry a high risk of chondrolysis.[253] However, data is limited for exposure from single injections. It is generally felt these carry substantially lower risk, but caution should be used in any patient who has received multiple single-dose injections as the additive effects are unclear.

Corticosteroids are no longer recommended to be used with intra-articular injections in the ED due to growing association with osteonecrosis, joint destruction, bone loss and acceleration of osteoarthritis.[254]

TECHNIQUE: After sterile preparation and following typical sterile technique, 10-20 mL of local anesthetic (typically lidocaine 1-2%) is injected directly into the joint capsule of the affected extremity. Ultrasound may improve success of procedure.[255]

HEMATOMA BLOCK

Injection of local anesthetic directly at the site of a fracture can be an effective option for pain control. Often referred to as a hematoma block, this type of infiltration can be used instead of or as an adjunct to regional anesthesia and can commonly be performed quickly using fracture landmarks. Typical locations include distal radius fracture and/or ulna fractures.

EVIDENCE: Injection of local anesthetic at the fracture site can be an effective option to allow manipulation and pain relief for patients with fractures. Typically, this is used for distal radius and/or ulna fractures. This can provide an alternative to regional anesthesia and may reduce the reliance on other medications, including those in ALTO pathways. Limited evidence suggests that a hematoma block provides equal pain relief compared to procedural sedation and may lead to reduced length of stay.[256,257]

Alternatives to Opioids for the Treatment of Pain continued

TECHNIQUE: Typically, 10-20 mL of local anesthetic (lidocaine 1%) is injected directly into the fracture site of the affected extremity, following sterile technique as in any other delivery of regional anesthesia. Ultrasound can also be used to improve success.

TRIGGER-POINT INJECTIONS

A focal area of spasm and inflammation (e.g., trapezius, rhomboid, low back) can be associated with chronic myofascial pain syndrome.

EVIDENCE: Indications for this approach include a palpable, taut band or nodule, reproducible pain with palpitation or a chronic painful condition, such as fibromyalgia.[258] Palpation of the trigger point should fully reproduce pain, which may be referred to other areas (e.g., nodule or taut band of spasm).[259] Dry needling will cause a disruption of the spastic feedback loop by interrupting abnormal activity in the sensory and motor nerve endings and muscle fibers.[260] Using local anesthetics, such as bupivacaine or lidocaine, with trigger point injections often resolves pain and decreases soreness. This technique may provide superior pain relief to alternative ALTO methods as well.[261]

TECHNIQUE: Local anesthetic is injected directly at the identified trigger point. Approach can vary from perpendicular, parallel to or at an angle to the skin depending on location and underlying structures (i.e., trigger points of the chest typically involve a parallel approach to avoid injury to the lung).

Instructional video found at the following link: https://cha.com/clinician-training-materials/

CERVICAL TRIGGER POINT INJECTIONS

Injection into the cervical trigger point deserves special attention as it has an ability to provide effective analgesia to a range of conditions, including musculoskeletal causes. This includes dental pain, headache, trigeminal neuralgia and other facial pain. Located in the paracervical musculature, the cervical trigger point is located one centimeter lateral and one centimeter vertical to the C6 spinous process.

EVIDENCE: Cervical trigger point injections have been found to be a successful treatment strategy for migraine headaches. There are also case reports of analgesia achieved in dental pain, trigeminal neuralgia and tension headaches.[262,263] Retrospective observational studies have shown therapeutic response in 85% of patients, with 65.1% achieving complete cessation of headache.[263]

TECHNIQUE: With the patient in the seated position, the cervical trigger point is found by palpating the C6 spinous process and moving one centimeter lateral and then one centimeter vertical. Following typical sterile technique for local anesthetic infiltration, 1.5 mL of local anesthetic (typically lidocaine or bupivacaine) is injected using a perpendicular approach to the skin at a depth of 1-1.5 inches.

Instructional video found at the following link: https://cha.com/clinician-training-materials/

Non-pharmacological Interventions in the ED Setting

Although few studies have assessed the benefit of nonpharmacologic, non-procedure-based therapies for the treatment of acute pain, such interventions carry little to no risk, may have potential benefit and can be safely adopted. A systematic review of the literature surveyed 56 studies on a range of nonpharmacologic interventions with pain reduction as an outcome.[264] Interventions that have been studied and shown to have potential value as analgesics in ED settings include physical therapy,[265] acupuncture,[266,267] heat/cold therapy,[268] massage,[269,270] music therapy,[271-274] educational videos[275,276] and brief cognitive behavior interventions.[277,278] The authors conclude that physical intervention, such as active mobilization and physical therapy, may produce early improvements in some pain conditions. Acupuncture, massage, transcutaneous electrical nerve stimulation and heat more consistently demonstrated immediate benefits in pain level, though the authors note that most studies were small with some risk of bias. Indirect interventions such as aromatherapy and hypnosis seemed to improve pain, while music therapy had mixed results in terms of pain benefit. Video, oral and written educational interventions tended to lessen pain. Of psychosocial interventions, very brief cognitive behavioral therapy (CBT) and short courses of CBT initiated in the ED were the most effective.

Alternatives to Opioids for the Treatment of Pain continued

SPECIAL POPULATIONS

ALTOs provide an excellent pathway for treatment of acute pain in the majority of patient populations. However, certain groups may have specific contraindications or cautions with many agents. ALTO pathways should be used as treatment suggestions and in no way replace clinical judgment, taking into account the appropriateness of each agent with thoughtful consideration of patient-specific factors such as, but not limited to:

AGE: Great care should be taken when treating elderly patients. The Beers Criteria is a well-established resource that can be used when considering treatment options for patients older than 65 years.[277] Some of the therapies suggested may pose a greater risk of adverse events or be inappropriate for use in the geriatric population and be used with extreme caution or avoided altogether, including but not limited to dicyclomine, haloperidol, diphenhydramine and muscle relaxants. This should be weighed against the increased risk of opioids and adverse events in this population as well. Non-pharmacologic adjuncts should be aggressively recommended including ice, heat, massage and physical therapy as appropriate. Topical medications, such as diclofenac and lidocaine, have less systemic absorption and side effects and should be strongly considered in this patient population.

RENAL DYSFUNCTION: Not all ALTO agents are safe to use for patients with renal dysfunction and are written to be dosed for a patient with presumed normal renal function. NSAIDs in particular should be avoided; in patients who cannot receive systemic NSAIDs, consider prescribing topical agents such as diclofenac gel or patches.

HEART FAILURE: Not all ALTO agents are recommended for use in patients with heart failure, particularly steroids and NSAIDs. In those patients where these agents should be avoided, consider prescribing topical applications or other alternatives.

PREGNANCY: ALTOs are not specifically designed for pregnant patients. Many of these agents are contraindicated in pregnancy, including but not limited to haloperidol, NSAIDs and valproic acid. However, some agents and ALTO procedures may be appropriate for use in pregnancy, and general ALTO principles can still be applied to this population.

CHILDREN: ALTOs are not specifically designed for children <15 years old or patients under 40 kg. ALTO principles can still be applied for this population, but pediatric precautions should be considered, and agents dosed appropriately. Though some agents may have efficacy and evidence in children, ALTO pathways have not been designed specifically for pediatric patients.

Alternatives to Opioids for the Treatment of Pain continued

ALTO Treatment Pathways

Headaches

INDICATION	FIRST-LINE AGENT	SECOND-LINE AGENT	DISCHARGE	PREVENTION
Migraine	Supplemental oxygen (15 L via NRB) for 15-20 minutes **+** Dopamine receptor antagonist: Prochlorperazine 10 mg IV ***OR*** Metoclopramide 10 mg IV **+** Dexamethasone 10 mg IV **+** Ketorolac 10 mg IV/15mg IM **+** 1 L 0.9% NS IV bolus **+/-** Cervical or trapezius trigger-point injection with 1% lidocaine or 0.25% bupivacaine ——— Diphenhydramine 25 mg IV has not been shown to prevent dystonic reactions but is an effective treatment when they occur	Sumatriptan 6 mg SC **+/-** Magnesium 1 g IV over 60 minutes **+/-** Antipsychotic: Haloperidol 2.5-5 mg IV ***OR*** Olanzapine 2.5-5 mg PO/ IV/IM ***OR*** Droperidol 1.25-2.5 mg IV **+/-** Valproic acid 500-1000 mg IV over 30 minutes **+/-** Lidocaine 1.5 mg/kg IV over 10 minutes (max 200 mg)	NSAID (Ibuprofen and diclofenac have most evidence for rapid resolution) **+/-** Sumatriptan 6 mg SC or 100 mg PO once as rescue **+/-** Reglan 10 mg PO every six hours **+/-** APAP/aspirin/ caffeine (Excedrin Migraine) PO every six hours	Counsel on medication overuse headaches (MOH); NSAIDs, APAP and other agents should not be used more than two times per week or 15 days per month ——— Barbiturates and opioids should be strongly avoided ——— Propranolol 40 mg PO BID ***OR*** Topiramate 25 mg PO at bedtime ***OR*** Magnesium 200 mg PO daily; titrate up to 600 mg PO daily as tolerated
Tension	APAP 1000 mg PO **+** Ibuprofen 400 mg PO ***OR*** Ketorolac 10 mg IV/15 mg IM	Cervical trigger-point injection **+/-** Cyclobenzaprine 5 mg PO	APAP 650 mg PO every six hours **+** Ibuprofen 400 mg PO every six hours	Counsel on MOH; NSAIDs, APAP and other agents should not be used more than two times per week or 15 days per month ——— Patient education sleep, lifestyle

Alternatives to Opioids for the Treatment of Pain continued

ALTO Treatment Pathways

Headaches continued

INDICATION	FIRST-LINE AGENT	SECOND-LINE AGENT	DISCHARGE	PREVENTION
Cluster	Supplemental oxygen (15 L via NRB) for 15 to 20 minutes **+** Sumatriptan 6 mg SC **+** Cervical or occipital trigger-point injection with 1% lidocaine or 0.25% bupivacaine **+** Prednisone 60 mg PO **+/-** 4–10% lidocaine via nasal atomizer, 2 mL intranasal (IN) bilaterally	Octreotide 100 mcg SC	Prednisone 10-day taper **+** Sumatriptan 6 mg SC once as rescue	Counsel on MOH; NSAIDs, APAP and other agents should not be used more than two times per week or 15 days per month ——— Verapamil 80 mg PO three times daily ***OR*** Topiramate 25 mg PO at bedtime ——— Referral to headache specialist for calcitonin gene-related peptide (CGRP) antagonist (galcanezumab)
Occipital neuralgia	Occipital nerve block with 1% lidocaine or 0.25% bupivacaine **+** Gabapentin 600 mg PO ***OR*** Carbamazepine 400 mg PO	APAP 1000 mg PO **+/-** Ibuprofen 400 mg PO ***OR*** Ketorolac 10 mg IV/15 mg IM	Gabapentin 300 mg PO three times daily **+/-** Ibuprofen 400 mg PO every six hours	Counsel on MOH; NSAIDs, APAP and other agents should not be used more than two times per week or 15 days per month ——— Carbamazepine 400 mg PO daily ——— Outpatient MRI to evaluate for compressive pathology
Trigeminal neuralgia	Transnasal sphenopalatine ganglion block with 4-10% lidocaine **+/-** Cervical trigger point injection with 1% lidocaine or 0.25% bupivacaine **+** Carbamazepine 400 mg PO ***OR*** Gabapentin 600 mg PO	Baclofen 40 mg PO **+/-** Ibuprofen 400 mg PO ***OR*** Ketorolac 10 mg IV/15 mg IM	Gabapentin 300 mg PO three times daily	Counsel on MOH; NSAIDs, APAP and other agents should not be used more than two times per week or 15 days per month ——— Outpatient MRA/MRI to evaluate for compressive pathology

Alternatives to Opioids for the Treatment of Pain continued

ALTO Treatment Pathways

Headaches continued

INDICATION	FIRST-LINE AGENT	SECOND-LINE AGENT	DISCHARGE	PREVENTION
Post-lumbar puncture	Caffeine 300-500 mg PO ***OR*** theophylline 250-300 mg PO (or aminophylline 250 mg IV over 20 minutes if NPO) **+** Gabapentin 600 mg PO **+** Hydrocortisone 100 mg IV	Anesthesia consult for blood patch	Caffeine either via beverages or tabs 100-300 mg PO daily **+** Gabapentin 300 mg PO three times daily **+** Prednisolone 20 mg PO daily for four days	N/A

Abdominal Pain

INDICATION	FIRST-LINE	SECOND-LINE	DISCHARGE
Inflammatory	APAP 1000 mg PO/PR **+** Ketorolac 10 mg IV/15 mg IM **+/-** Ketamine 0.1-0.3 mg/kg IV over 10 minutes (or 0.1 mg/kg/hr IV until desired analgesia)	Haloperidol 2.5-5 mg IV/IM **+/-** Lidocaine 1.5 mg/kg IV over 10 minutes (max 200 mg)	APAP 650 mg PO every six hours **+/-** Ibuprofen 400 mg PO every six hours **+/-** Dicyclomine 20 mg PO every six hours
Peptic ulcer or gastritis	Famotidine 40 mg IV/PO **+** GI cocktail (e.g., aluminum hydroxide-magnesium hydroxide/viscous lidocaine/ diphenhydramine)	Ketamine 0.1-0.3 mg/kg IV infusion over 10 minutes (or 0.1 mg/kg/hr IV until desired analgesia)	Proton pump inhibitor **+/-** Aluminum hydroxide-magnesium hydroxide **+/-** Viscous lidocaine **+/-** treatment of H. Pylori if indicated
Spasmodic	Dicyclomine 20 mg PO/IM **+** Ketorolac 10 mg IV/15 mg IM **+** APAP 1000 mg PO/PR	Haloperidol 2.5–5 mg IV/IM **+/-** Ketamine 0.1-0.3 mg/kg IV over 10 minutes (or 0.1 mg/kg/hr IV until desired analgesia)	Dicyclomine 20 mg PO every six hours **+/** APAP 650 mg PO every six hours

Alternatives to Opioids for the Treatment of Pain continued

ALTO Treatment Pathways

Abdominal Pain continued

INDICATION	FIRST-LINE	SECOND-LINE	DISCHARGE
Chronic functional	Haloperidol 2.5-5 mg IV/IM **+** Dicyclomine 20 mg PO/IM **+/-** Ketorolac 10 mg IV/15 mg IM	Olanzapine 2.5-5 mg ODT/IV/IM **+/-** Lidocaine 1.5 mg/kg IV over 10 minutes (max 200 mg)	*Consider One of the Following:* Duloxetine 30 mg PO once daily for one week, then increase to 60 mg once PO daily as tolerated ***OR*** Venlafaxine *extended release:* Initial: 37.5 mg or 75 mg PO once daily; increase by 75 mg each week to a maximum dosage of 225 mg PO once daily based on tolerance and effect ***OR*** Nortriptyline 12.5 mg PO once daily at bedtime; may increase as tolerated up to 35 mg per day Assure patient has timely PCP follow-up within one week of initiation of amine reuptake inhibitor or tricyclic antidepressant
Cyclic vomiting syndrome / Cannabis hyperemesis syndrome	Haloperidol 2.5-5 mg IV/IM **+** Dicyclomine 20 mg PO/IM **+/-** Capsaicin 0.1% cream applied in a thin layer to abdomen	Lidocaine 1.5 mg/kg IV over 10 minutes (max 200 mg) **+/-** Ketamine 0.1–0.3 mg/kg IV over 10 minutes (or 0.1 mg/kg/hr IV until desired analgesia) **+/-** Metoclopramide 10 mg IV ***OR*** Prochlorperazine 10 mg IV **+/-** Diphenhydramine 25 mg IV **+/-** Olanzapine 5 mg ODT/IV/IM	Olanzapine 5 mg ODT three to four times daily PRN nausea, vomiting and/or pain **+** Dicyclomine 20 mg PO every six hours PRN pain **+** Capsaicin 0.1% cream applied to abdomen four times daily PRN pain **+** *Consider one of the following:* Duloxetine 30 mg PO once daily for one week, then increase to 60 mg PO once daily as tolerated ***OR*** Venlafaxine *extended release:* Initial: 37.5 mg or 75 mg PO once daily; increase by 75 mg each week to a maximum dosage of 225 mg PO once daily based on tolerance and effect ***OR*** Nortriptyline 12.5 mg PO once daily at bedtime; may increase as tolerated up to 35 mg per day Assure patient has timely PCP follow-up within one week of initiation of amine reuptake inhibitor or tricyclic antidepressant

Alternatives to Opioids for the Treatment of Pain continued

ALTO Treatment Pathways

Abdominal Pain continued

INDICATION	FIRST-LINE	SECOND-LINE	DISCHARGE
Renal colic	Ketorolac 10 mg IV/15 mg IM **+** APAP 1000 mg PO/PR **+** Lidocaine 1.5 mg/kg IV over 10 minutes (max 200 mg)	Desmopressin 40 mcg IN **+/-** Ketamine 0.1-0.3 mg IV over 10 minutes or 0.5 mg/kg IN (max 50 mg) **+/-** Dicyclomine 20 mg PO/IM	Scheduled NSAIDs and APAP (e.g., ibuprofen 400 mg PO every six hours + APAP 650 mg PO every six hours until definitive treatment) **+/-** Tamsulosin 0.4 mg PO daily until stone passage **+/-** Desmopressin 0.4 mg PO daily (for those who cannot tolerate NSAIDs)
Additional considerations	• Abdominal pain associated with nausea often benefits from haloperidol or olanzapine, both of which have antiemetic and antinociceptive properties. • NSAIDs should be avoided in cases of suspected peptic ulcer disease (PUD) and previous gastric bypass. • NSAIDs, including ketorolac, are safe for use prior to most abdominal surgeries and do not increase bleeding risk.[280,281]		

Alternatives to Opioids for the Treatment of Pain continued

ALTO Treatment Pathways

Musculoskeletal Pain

INDICATION	FIRST-LINE	SECOND-LINE	DISCHARGE
Muscle strain, spasm, hematoma, neuropathy	APAP 1000 mg PO **+** Ibuprofen 400 mg PO OR Ketorolac 10 mg IV/15 mg IM **+** Lidocaine 5% patch **+/-** Trigger-point injection with 1% lidocaine or 0.25% bupivacaine **+/-** Cyclobenzaprine 5-10 mg PO	Ketamine 0.1-0.3 mg IV over 10 minutes (or 0.1 mg/kg/hr IV until desired analgesia) ***OR*** 0.5 mg/kg IN (max 50 mg) **+/-** If neuropathic component: Gabapentin 300-600 mg PO **+/-** Lidocaine 1.5 mg/kg IV over 10 minutes (max 200 mg)	APAP 650 mg PO every six hours **+** Ibuprofen 400 mg PO every six hours ***OR*** Topical Diclofenac 1% gel (if cannot tolerate oral NSAIDs) **+/-** Cyclobenzaprine 5–10 mg PO three times daily **+/-** Lidocaine 5% patch every 24 hours ***OR*** Topical menthol gel over-the-counter (OTC) **+/-** *If neuropathic pain, choose one:* Gabapentin 300 mg PO three times daily ***OR*** Pregabalin 75 mg PO twice daily ***OR*** Duloxetine 30 mg PO once daily for one week, then increase to 60 mg PO once daily as tolerated ***OR*** Venlafaxine *extended release:* Initial: 37.5 mg or 75 mg PO once daily; increase by 75 mg each week to a maximum dosage of 225 mg PO once daily based on tolerance and effect ***OR*** Nortriptyline 12.5 mg PO once daily at bedtime; may increase as tolerated up to 35 mg/day
Extremity fracture/ Dislocation	Hematoma block/regional anesthesia **+** APAP 1000 mg PO **+** Ibuprofen 400 mg PO ***OR*** Ketorolac 10 mg IV/15 mg IM	Ketamine 0.1-0.3 mg IV over 10 minutes ***OR*** 0.5 mg/kg IN (max 50 mg) **+/-** Nitrous oxide inhaled titrated up to 70%	APAP 650 mg PO every six hours **+** Ibuprofen 400 mg PO every six hours

Alternatives to Opioids for the Treatment of Pain continued

ALTO Treatment Pathways

Dental Pain

INDICATION	FIRST-LINE	SECOND-LINE	DISCHARGE
Dental pain from cavity, fracture, abscess	APAP 1000 mg PO **+** Ibuprofen 400 mg PO **+** Dental block or regional block with 0.25–0.5% bupivacaine with epinephrine **+/-** Pretreatment of topicalize mucosa with 20% benzocaine or 5-10% lidocaine applied via cotton ball or swab to mucosa five to 10 minutes prior to procedure	Dexamethasone 8 mg PO/IM **+/-** Gabapentin 600 mg PO ***OR*** Pregabalin 150 mg PO	APAP 650 mg PO every six hours **+** Ibuprofen 400 mg PO every six hours **+** 2% viscous lidocaine topical (apply via cotton ball to affected area)

Harm Reduction

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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 negative consequences associated with illicit drug use. The 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 drugs by logical physician counseling. The simplistic directive to "stop using because you may die" or suffer a complication is ineffective and often deleterious to the physician-patient relationship. In reality, patients must possess the internal resolve to pursue recovery, and that process is best aided 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 primarily has been used in recent years for the treatment of people who inject drugs (PWID); however, its principles are broadly applicable to most patients with SUD. Injection drug use is intertwined with the opioid epidemic as roughly 75% of injection heroin addictions originate with prescription opioids.[282] As rates of opioid prescribing have decreased, many patients with opioid use disorders have turned to the illegal drug market to obtain opioids.

Harm reduction aims to prevent the spread of infection, including HIV/AIDS, hepatitis B and C, sepsis and endocarditis; reduce the risk of overdose and other drug-related fatalities; and decrease the negative effects that drug use may have on individuals and communities.

Of the thousands of patients who present with opioid-related health concerns – ranging from withdrawal to constipation to overdose to injection-related infections – most are not ready to quit on the day they visit the hospital. Given the unprecedented scope and destruction of the opioid epidemic, clinicians can and should do better in counseling and treating the addicted patient who is not ready to stop using.

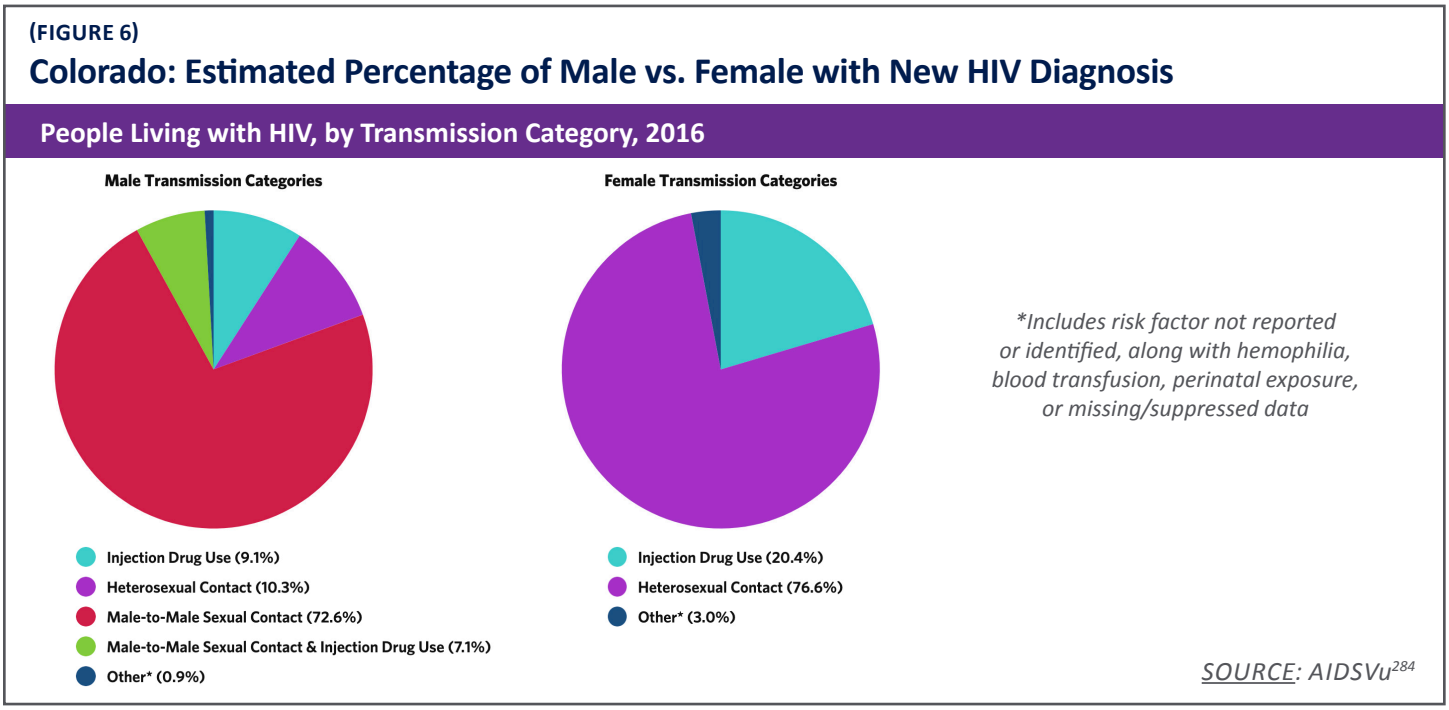
High Stakes: The Risks of IV Drug Use and Infectious Complications

HIV

In 2016, injection drug use directly accounted for 9% of new HIV diagnosis, 13% of new AIDS diagnosis and is believed to have contributed to approximately 20% of new HIV/AIDs diagnosis.[283] In Colorado, 24% of new HIV diagnoses in women and 17.4% of new HIV diagnoses in men are associated with injection drug use **(FIGURE 6)**.

(FIGURE 6)

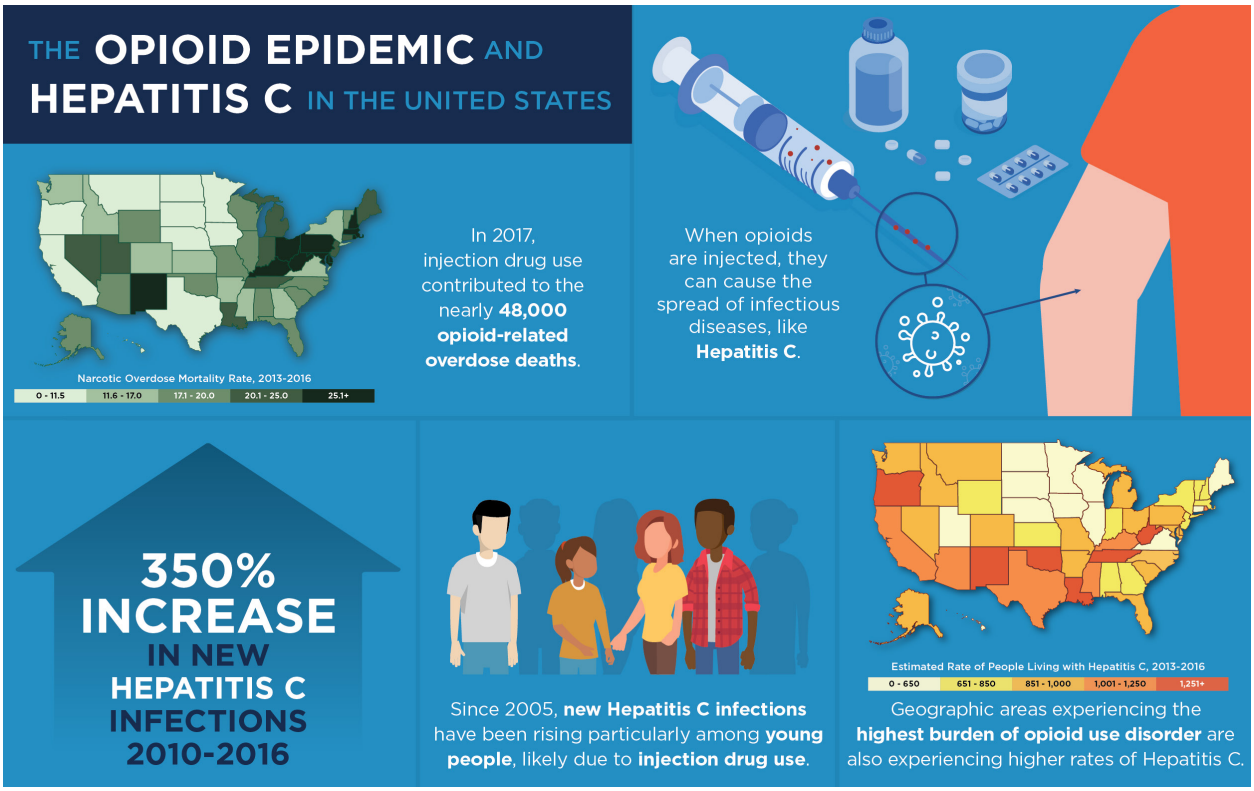
Colorado: Estimated Percentage of Male vs. Female with New HIV Diagnosis



SOURCE: AIDSVu[284]

(FIGURE 7)

The Opioid Epidemic and Hepatitis C in the United States



SOURCE: HEPVu[290]

HEPATITIS B AND C

Injection drug use accounts for the majority of new hepatitis C (HCV) infections.[285] According to the CDC, acute HCV infections increased about 3.5-fold from 2010 to 2016 (from 850 to 2,967 reported cases).[286] This increase in new HCV infections is associated with rising rates of injection drug use.[285] Most cases of acute HCV are not reported, as few patients with HCV have symptoms, and only a minority of them are diagnosed. After adjusting for this underdiagnosis, the CDC estimates that 41,200 new HCV infections occurred in 2016.[286] In regard to hepatitis B, of the 1,371 case reports of hepatitis B in 2016, over 34.4% of cases indicated use of injection drugs.[287] In Colorado, the age-adjusted HCV rate increased by 129% from 2012 to 2016 (most attributed to IV drug use [IVDU]) with 894 new cases in 2016 alone.[288]

Hepatitis B and C represent a growing public health crisis. They place patients at high risk for developing cirrhosis, liver failure and hepatocellular carcinoma. HCV, once an untreatable disease, has become curable with new medications such as sofosbuvir or combination medications such as ledipasvir/sofosbuvir. However, these treatments often cost over $80,000 per regimen, placing significant strain on medical systems and payers.[289]

ENDOCARDITIS

Once a rare infectious disease, bacterial endocarditis rates 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).[291] Cases of infectious endocarditis are increasing in association with the current opioid epidemic and affect young Caucasian people from rural areas most.[292-294] A CDC report from North Carolina found that the incidence of hospitalizations for endocarditis among drug-dependent patients has increased twelve-fold from 2010 to 2015 and associated health care costs increased eighteen-fold.[295] Similar increases are occurring

Harm Reduction continued

in Colorado, where Centura Health reported a system-wide increase in IVD-related endocarditis from four cases in 2012 to 66 cases in 2017.[296] Endocarditis places significant strain on patients, health systems and payors. 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 among persons on Medicaid or without insurance.[295]

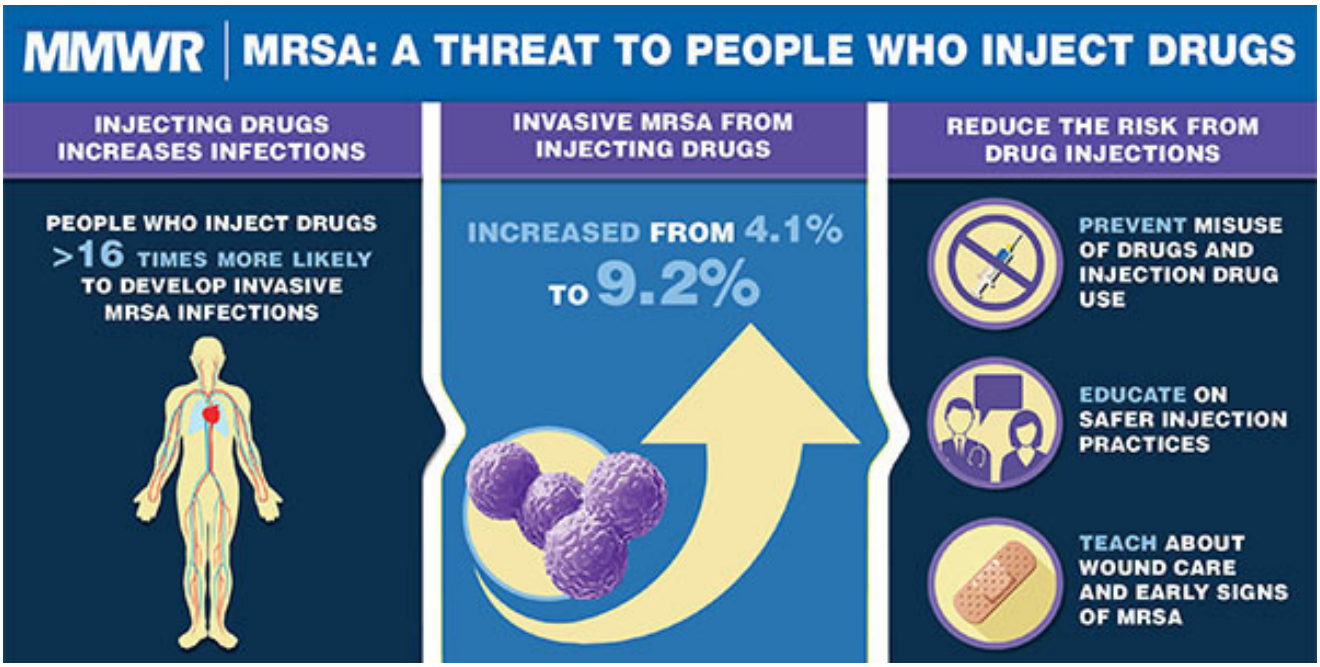
INVASIVE BACTERIAL INFECTIONS

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% (or 54) developed injection-related cellulitis or an abscess.[297] More significant infections such as wound botulism, osteomyelitis, epidural abscess, necrotizing fasciitis and invasive methicillin-resistant Staphylococcus aureus (MRSA) have all been linked to IVDU. A 2018 CDC report found that PWID were 16.3 times more likely to develop invasive MRSA infections. 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.[298]

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 burden of serious bacterial infections related to IVDU at $700 million per year in 2012.[292] As IVDU has continued to grow, so have the financial burdens, as well as the toll on community health.

(FIGURE 8)

MRSA: A Threat to People Who Inject Drugs (PWID)



SOURCE: CDC MMWR[298]

Harm Reduction continued

STIGMA AND BIAS AS OBSTACLES TO HEALTH CARE

Drug addiction is a medical disease, defined by genetic predisposition and long-term changes in brain structure and function. Clinically, patients often suffer from uncontrollable, compulsive drug cravings that render them powerless, even in the face of catastrophic social and health-related consequences.[299] Health care professionals have been shown to view patients with substance abuse disorders negatively and can behave in a manner toward them that erodes both clinician empathy and patient care.[300] As a result, patients who inject drugs often go to great lengths to avoid medical care, including signing 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 medical care 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, which address the obstacles created by stigma these patients face **(TABLE 8)**.

It is important to recognize the behavioral components of SUD and the frequent comorbidities of pain, anxiety and depression. These often require clinicians to aid patients in developing the internal drive and resiliency needed to make sustainable adjustments in behavior. This process can be successfully guided by formative rather than punitive approaches. Motivational interviewing techniques, cognitive behavioral therapy, dialectical behavioral therapy and other counseling/therapy methods have been shown to be effective, particularly when paired with appropriate MAT and a collaborative harm reduction-minded approach.[301-303]

Evidence-based harm reduction strategies, rather than fear and stigma-driven ultimatums, improve patient and community outcomes.[304] Providing effective care for PWID requires a significant investment of time, effort and specialized knowledge. For providers who are unable to

(TABLE 8)

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 this negativity and condescension, many drug users avoid seeking health care by trying to "doctor" themselves.
- Respect patients 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 them 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. However, these insensitive "Look at the crazy thing this junkie did to herself/himself!" conversations are inappropriate and promote a feeling of shame in the patient.
- Contacting authorities to report illegal substance use is a violation of the Health Insurance Portability and Accountability Act (HIPAA) and patient privacy. If law enforcement needs to be contacted (e.g., a mandatory reporting of assault with a deadly weapon), advise the patient of that plan.
- Post-discharge planning should be conducted with the patient to avoid vague or unrealistic aftercare plans. Specifically, addressing and creating options for non-medical needs can promote improved adherence to medical treatment.
- Provide targeted educational information about risk reduction rather than judgmental speeches or shaming lectures about drug use.

provide the degree of time, effort or knowledge these patients require, additional resources and support should be mobilized to meet patients' needs. Some of these resources are listed in **APPENDIX IV, MAP AND LISTING OF SYRINGE ACCESS PROGRAMS IN COLORADO**.

Harm reduction and therapeutic relationship-building is especially critical in communities where buprenorphine and methadone treatment programs are scarce and plagued by long waiting lists. Additionally, emergency physicians may be unfamiliar with harm reduction principles, unaware of how to perform effective interventions or lack 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 and not a moral failure. Caregivers should endeavor to meet patients where they are, infusing empathy and understanding into the patient/provider relationship. Behavioral changes should be encouraged but addressed with understanding and patience, incorporating patients' motivations and goals.**
   a. Seek out educational opportunities to better understand addiction and end the stigma associated with opioid use disorders.
   b. A harm reduction mentality should incorporate the following:
      i. Humanism: Seek to accept and understand patients without moral judgments.
      ii. Pragmatism: Abstinence is an ideal and not prioritized – target messaging toward harms and concerns over health rather than moral/societal standards.
      iii. Individualism: See the patient as an individual.
      iv. Autonomy: Respect patients' decisions.
      v. Incrementalism: Small step-by-step improvements often 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 a provider's medical advice, termination of the relationship often will cause the patient harm.
   c. Counsel patients and allow them to seek treatment—or not—at their own pace **(TABLE 9)**. Pressuring or forcing patients into treatment for SUD is ineffective, violates patient autonomy and creates an adversarial rather than therapeutic relationship.

(TABLE 9)

Counseling Patients with Opioid Use Disorders

DO	DON'T
• Use respectful language when discussing patients' 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 to the needs of the patient.	• Don't use negative terminology such as "addict" or "junkie." • Don't tell patients they are ruining their lives or are "going to die." • Don't attempt to pressure patients to begin substance abuse treatment. • 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 patients are treated.

Harm Reduction continued

2. **Emergency physicians are encouraged to be knowledgeable about how to prevent overdose in PWID and patients who misuse prescription opioids. Consider counseling patients on the following safe practices prior to discharge:**
   a. Avoid using alone.
      i. Overdoses that occur when patients use alone can result in death.
      ii. Drug users should be encouraged to inject in the presence of others for safety. Colorado's Good Samaritan law protects individuals who call 911 to report an overdose, exempting them and the patient from arrest and prosecution for small drug charges.
   b. Always carry naloxone.
      i. The evidence in support of naloxone is staggering. Since 1996, the opioid reversal agent has saved more than 26,000 lives.[305]
      ii. Due to the fact that most overdoses are witnessed and transpire over hours, naloxone is patients' most powerful tool for preventing overdose death.
      iii. Naloxone is safe and effective both in and out of the hospital.
      iv. Numerous studies over the past 20 years have confirmed that laypeople can administer naloxone outside of a hospital with therapeutic success.[305-309]
      v. The antidote should be dispensed in the hospital to anyone suspected of abusing IV drugs and at-risk patients should be encouraged to keep the naloxone within reach at all times.
   c. If injecting heroin or fentanyl, try test shots.
      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, patients should use a small test 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 use the same dose after a period of abstinence, which often occurs after hospitalization, incarceration or a period of sobriety.
   f. Fentanyl testing strips have been recommended by some harm reduction organizations as a method to identify heroin that is laced with fentanyl or fentanyl analogues. This can be considered by hospital clinicians and hospitals based on their research of the evidence and prevalence of fentanyl in their communities.

3. **Every emergency medicine physician is encouraged to be well-versed in the safe injection of heroin and other intravenous drugs so they can communicate with patients about drug use practices and inquire about potential unsafe habits.**
   a. Heroin is cheap and widely available. Patients addicted to prescription opioids often turn to heroin for economic reasons or due to its faster and more intense high. Heroin's increasing popularity has caused a rise in communicable (e.g., HIV and hepatitis C and B) and noncommunicable diseases (e.g., abscesses, cellulitis and endocarditis).
   b. Heroin comes in two forms: a white powder (often called China White) and black tar. China White is easily smoked while black tar heroin is not. In Colorado, most heroin is black tar, which must be injected in order to be effective in generating a high or withdrawal relief.
   c. 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.
   d. The vast majority of medical providers are unfamiliar with drug injection methods and are ill-prepared to discuss safeguards with PWID. Providers are encouraged to be familiar with the equipment used to inject heroin and IV drugs (Appendix II). Perhaps most importantly, clinicians may need to know the steps to injecting drugs, what common and unsafe practices are associated with each step and how to mitigate risk **(APPENDIX III)**.
   e. Most PWID learn from their peers and often learn unsafe and dangerous habits. It is important for clinicians to be able to engage patients, identify unsafe practices and educate patients on safer injection practices.

Fentanyl Testing Strips

Fentanyl is an opioid medication that is 50-100 times more potent than morphine.[310] A significant amount of heroin has been found to contain some amount of fentanyl; a recent study among 242 heroin users in British Columbia, Canada, found that 29% tested positive for fentanyl and 73% of these users did not know they were using fentanyl.[311] This inadvertent use of fentanyl by many heroin users has contributed to the rise in overdose 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 the desire to know if their drugs contain fentanyl.[312] 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%.[313] BTNX can detect other fentanyl analogues including carfentanil, acetylfentanyl, butyrylfentanyl, 3-methylfentanyl, ocfentanil and sufentanil.[313]

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

At this time, CO's CURE and Colorado ACEP take no position on the use of fentanyl testing strips as part of harm reduction care for OUD.

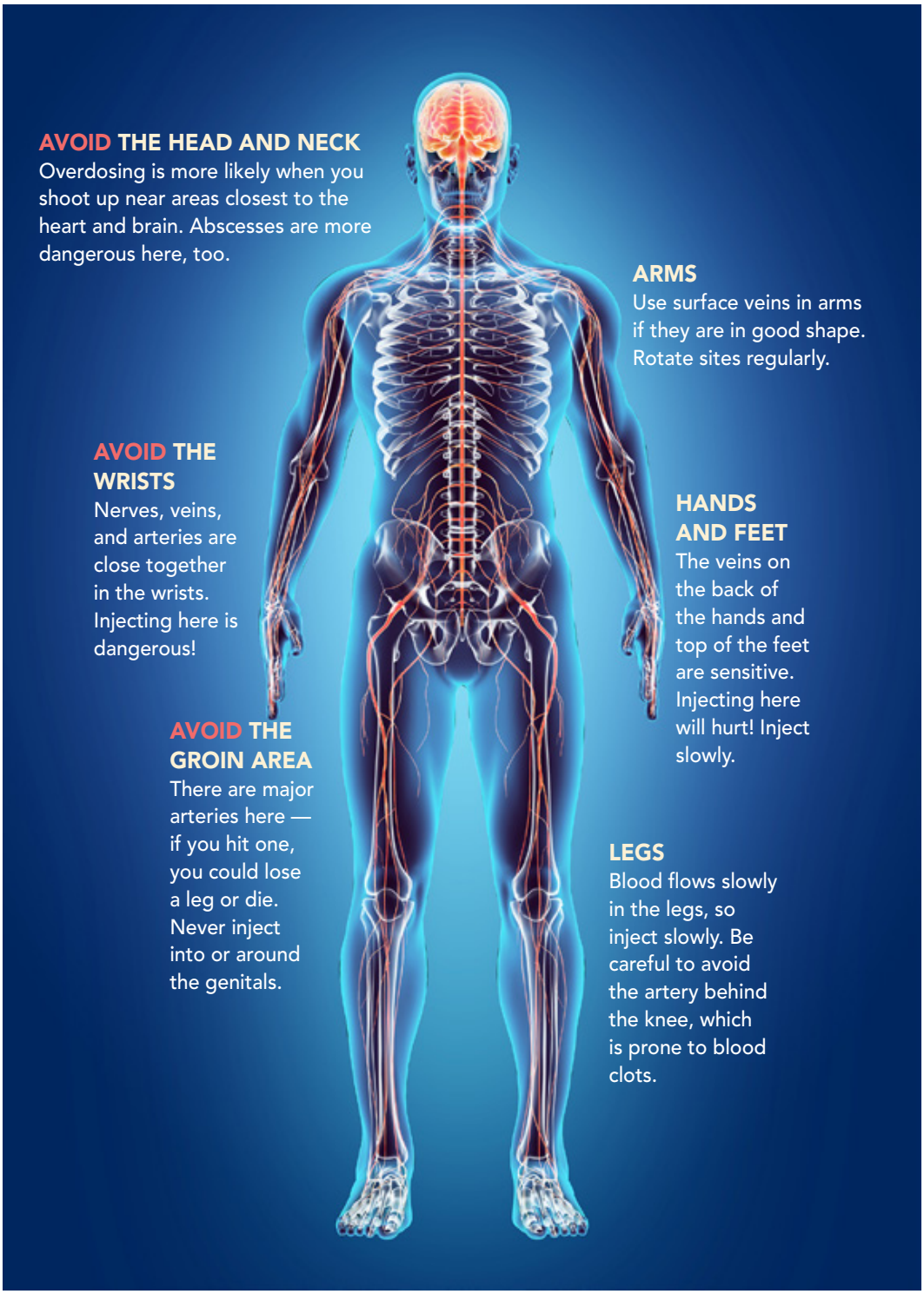
4. **Emergency physicians should be knowledgeable about how to prevent communicable diseases such as HIV, hepatitis B and hepatitis C in PWID. These patients should be counseled on safe practices prior to discharge.**
    a. Data collected by HRAC estimates that 24% of PWID are hepatitis C positive. Injection drug use is the leading transmission method of HCV in the United States.
    b. A notorious HIV outbreak in one rural 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 HIV in 2015 when 235 new cases were diagnosed – all attributed to a local epidemic of injection oxymorphone use.[314]
    c. Caution patients against 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 filters/cottons). **(FIGURE 7)**
        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 with bleach.
        i. The cleaning solution should be nine parts water to one part bleach. Syringes and needles should be actively rinsed then soaked.
        ii. Materials should be rinsed and soaked for two minutes at minimum and optimally 10 minutes; the longer they 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 afterwards.

Harm Reduction continued

5. **Emergency physicians are encouraged to be knowledgeable about how to prevent soft tissue infections and serious invasive bacterial infections in PWID. Providers may wish to educate patients on the following safe 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.
      ii. Patients can obtain new equipment for free through local syringe access programs (formerly referred to as needle exchange programs).
      iii. If such resources are unavailable, advise patients to purchase needles, syringes and alcohol pads at pharmacies.
      iv. As a last resort, if a patient must reuse equipment, it should be cleaned with bleach.
      i. Syringes should be rinsed with water, disinfected with pure bleach, then rinsed with clean water.
      ii. All equipment should be cleaned, not just syringes and needles.
      iii. The CDC provides a handout that can be shared with patients: https://www.cdc.gov/hiv/pdf/library/factsheets/cdc-hiv-clean-your-syringes.pdf
   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 drank 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. If these are unavailable, water should be sterilized by heating it at rolling boil for 10 minutes and allowing it to cool.
   d. Avoid "skin popping" or "muscling," where heroin or other drugs are not injected into the vein but into subcutaneous tissue or muscles. This predisposes to abscesses and soft tissue infections.
6. **Emergency physicians are encouraged to be knowledgeable about how to prevent vein sclerosis and preserve veins in PWID. Providers may wish to counsel patients on safe practices prior to discharge.**
   a. Patients should be advised to use highest gauge (smallest) needle possible, and to rotate injection sites starting distally.
   b. Patients should be encouraged to drink water to remain well hydrated. If an acidic solution is required to dissolve product, use citric acid – never lime, lemon or orange juice, which are more sclerotic and carry a higher risk of infection.
   c. Advise against using the jugular, femoral or pedal veins, which can further increase the danger of infection **(FIGURE 9)**.
   d. Getting Off Right is a good resource for PWID, written collaboratively by medical professionals and people who use drugs.

(FIGURE 9)

Safer Injecting for Patients Who Inject Drugs



SOURCE: 2017 Colorado ACEP Opioid Prescribing & Treatment Guidelines[42]

Harm Reduction continued

7. **Ideally, all patients who receive prescriptions for opioids and those who have been diagnosed with SUD or a related medical issue are 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 encouraged to be provided:
      i. Using unmeasured, potentially toxic substances and their combinations is very dangerous. If abstinence is not an option then precautions for overdose, prevention of infection and protecting veins should be followed (see previous section).
      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 the 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 leading to drug-induced paranoia/psychosis, anxiety and panic attacks among other complications. Counsel patients to seek medical attention if these symptoms present.

8. **All patients who inject drugs are encouraged to 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.[315]
   b. The additional resources these centers often provide (e.g., sterile water, cooking units and cleaning solutions) can also help reduce such dangers.
   c. The World Health Organization (WHO) suggests a "compelling case that needle and syringe programs substantially and cost effectively reduce the spread of HIV among PWID and do so without evidence of exacerbating injecting drug use at either the individual or societal level."[316]
   d. In 2000, the American Medical Association (AMA) adopted a position strongly supporting the efficacy of these programs when combined with addiction counseling.[317]
   e. An online list of local syringe access/harm reduction programs can be found through the North American Syringe Exchange Network. See **APPENDIX IV**, Map and Listing of Syringe Access Programs in Colorado (updated September 2019).

Harm Reduction continued

9. **Emergency physicians are encouraged to work with hospitals to establish take-home naloxone programs to provide high-risk patients with naloxone at discharge. If naloxone cannot be given at the time of release, patients can receive a prescription and be informed about the over-the-counter availability of naloxone in many Colorado pharmacies.**
   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, the CDC and the 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 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."[318]
   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.[319]
   c. PWID have contact with other people at risk. While patients will rarely rescue themselves with naloxone, they can often use naloxone to rescue others who may have inadvertently overdosed.
   d. Family members and friends, with patients' permission, should be counseled on recognizing overdose and using naloxone.
   e. The risk of 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.[320]
   f. Pharmacies that participate in Colorado's standing order naloxone protocols can be found at www.stoptheclockcolorado.org.

(TABLE 10)

Naloxone is recommended to be given or prescribed to the following high-risk patients at discharge:

Ready-to-use naloxone is recommended to be given directly to high-risk patients at discharge who:

- Receive care for opioid intoxication or overdose.
- Have suspected substance abuse or nonmedical opioid use.
- Are taking >50 mg morphine equivalents per day.
- Are receiving an opioid prescription for pain, AND
  - 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 released from incarceration.
- Have resumed opioid use after a period of abstinence.

Harm Reduction continued

10. Emergency physicians may wish 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), which was passed in 2013, 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 Good Samaritan Laws (Colorado Revised Statute § 18-1-711 and Colorado HB 16-1390):
   i. Samaritan acting in good faith
   ii. No arrest or prosecution for possession
   iii. No arrest or prosecution for paraphernalia and protection from other crimes

c. Standing Orders for Naloxone (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 those who might benefit from it the most, including:
      - A family member, friend or other person in a position to assist a person at risk of overdose
      - An employee or volunteer of a harm reduction organization
      - A first responder
      - An individual at risk of overdose

C. Additional resources: https://www.colorado.gov/cdphe/naloxoneorders

11. It is recommended that all patients who receive prescriptions for opioids be educated on their risks, safe storage methods and the proper disposal of leftover medications.

a. Most patients who misuse opioids receive them from friends and/or family.[321]

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

c. Once acute pain has resolved and medication is no longer required, it is critical to dispose of unused medication promptly.

d. If disposing of medication at home, patients should 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 inedible (e.g., kitty 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.[322]

e. An increasing number of communities also offer prescription take-back programs. Patients should be encouraged to use one of the preferred disposal locations found on www.takemedsback.org or participate in a national DEA-sponsored take-back event. More than 50% of the counties in Colorado offer safe disposal sites for controlled substances, and the number of these facilities is increasing rapidly.

f. Additional Resources
   - http://www.takemedsseriously.org
   - http://www.corxconsortium.org/wp-content/uploads/Safe-Disposal-Brochure.pdf
   - http://www.deadiversion.usdoj.gov/drug_disposal/takeback/index.html

Harm Reduction continued

Policy Recommendations

1. **Harm reduction agencies and community programs that provide resources for PWID should be made readily available.**
   a. The passage of Colorado Revised Statute § 25-1-520 in 2010 legalized the establishment of syringe access programs with local jurisdiction approval.
   b. Community programs aimed at 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. These programs, many of which also provide basic medical and social services to this high-risk population, should 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 safe syringe exchanges.**
   a. Colorado SB 19-227 allows for syringe access out of hospitals and EDs, limiting liability.
   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. Emergency physicians 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 foster harm reduction.
   e. Ideally, such initiatives should be funded by national or state governments, nonprofit organizations or grants to make this service cost effective for participating hospitals.

Treatment of Opioid Use Disorder

c|h|a
Colorado Hospital Association

COLORADO
MEDICAL SOCIETY

COLORADO
CONSORTIUM
for Prescription Drug Abuse Prevention

Treatment of Opioid Use Disorder

Of the estimated 2.1 million people in the United States with OUD, fewer than 20% receive evidence-based treatment with MAT.[323] The consequences of this treatment gap are substantial, including dramatically increased risks of overdose injury and death; transmission of HIV, viral hepatitis and invasive bacterial infections; and a range of risky and criminal behaviors. It is now recognized 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 and have relapse rates of greater than 80%.[324] 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.[325] As many emergency physicians are aware, a quarter or more of patients with OUD will leave the hospital against medical advice due to craving, withdrawal, fear of stigma, mistreatment or social pressures.[326] Patients whose withdrawal is managed with buprenorphine or methadone are less likely to leave against medical advice and have shorter, less complicated admissions.[327,328] Finally, patients with OUD have been shown to have an increased risk of overdose death following a hospitalization during which they did not receive opioid agonist treatment.[329] Emergency physicians are ideally positioned to help people with untreated OUD access care, as they are among the few health professionals that may come into contact with many of these patients. The stigma surrounding OUD leads some patients to conceal their disease, and past negative experiences with the health care system make other patients wary of medical providers. Emergency physicians working today have an opportunity to radically change how they treat this patient population. Emergency physicians can screen patients consistently and offer help to patients with OUD in a non-stigmatizing, compassionate manner. Finally, emergency physicians can establish practices and protocols so that any patient who wants to initiate MAT can do so. Patients started on buprenorphine in the ED are more than twice as likely to be in treatment one month later than patients who are only given referrals.[330] By adopting these novel approaches, emergency physicians can make an enormous contribution to improving the lives of people with OUD.

Practice Recommendations

1. **Emergency physicians should be well versed in diagnosing patients with OUD.**
   a. OUD and SUD 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 of Americans under the age of 50 years, fewer than 10% of medical schools provide a formal addiction curriculum.[331]
   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.

(TABLE 11)

Summarized DSM-5 Diagnostic Categories and Criteria for OUD

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[332]

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 often exhibit pharmacological dependence but would not necessarily be considered to have OUD.

e. 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.[333]

f. Abstinence-based therapies are largely ineffective for the treatment of OUD. Emergency physicians should not routinely recommend abstinence-based treatments for OUD.[334]

g. Like many of the conditions emergency physicians encounter, OUD is a chronic, relapsing disease. Just as emergency physicians treat the underlying disease of a diabetic with neuropathy, patients presenting with complications of OUD should be treated for OUD.

h. Emergency clinicians are advised to educate patients about OUD during their ED visit. Patients with OUD benefit from learning that OUD is a chronic disease in which the brain is changed. 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 medications contribute to disease management and recovery. Patients with OUD should know that treatment with buprenorphine or methadone will make them feel more comfortable and reduce their risk of overdose upon discharge.

i. Treatment with buprenorphine or methadone for OUD can be maintained for years or be a lifelong drug. Clinicians are encouraged to tell patients to anticipate treatment that may last years or a lifetime.

j. Buprenorphine or methadone treatment should not be prematurely tapered. OUD is a chronic, relapsing disease for which most patients require ongoing treatment. Management of MAT should be coordinated with an addiction specialist or the patient's primary care provider.
k. Patients on appropriate therapeutic doses of methadone or buprenorphine are cognitively normal and function normally in society.
l. 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.
m. Most patients with OUD are not adequately treated. As of 2019, the Colorado Office of Behavioral Health estimated a treatment gap of approximately 70%, with only 30% of patients with OUD receiving treatment.
n. Patients and providers should be educated that relapse in OUD is common, manageable and not a contraindication to future trials of treatment. Patients with OUD have similar medication adherence and relapse rates as patients with other chronic diseases such as diabetes, asthma and hypertension.[335]

2. Emergency physicians should consider screening all patients for OUD and SUD.

a. While some patients present with a clear diagnosis of OUD, many patients with addiction 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 an SUD by their hospital treatment teams.[336] The stigma surrounding OUD prevents many patients from providing a full history.
b. Emergency physicians should 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. A 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 (www.sbirtcolorado.org) 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. For those unfamiliar with diagnosing OUD, the Rapid Opioid Dependence Screen (RODS) can be administered and scored in two to three minutes. For the RODS screen, 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 at www.integration.samhsa.gov/clinical-practice/motivational-interviewing.
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 may require more specific testing with chromatography. False positive tests can be seen in patients ingesting poppy seeds or taking medications such as quinolones and rifampin.
   ii. PDMP monitoring should be routinely performed, though many patients with OUD will have no reported prescriptions in the database. Among nonmedical users of opioids, over 70% acquire opioids from friends, family or illicit purchase.[337]

Treatment of Opioid Use Disorder continued

3. **ED clinicians should strongly consider offering MAT with buprenorphine or buprenorphine/naloxone to patients with untreated OUD.**
   a. Methadone, buprenorphine and naltrexone are the three FDA-approved medications for the treatment of OUD. Methadone is a full opioid agonist and buprenorphine is a partial agonist. Methadone and buprenorphine are sometimes termed "opioid agonist treatments" to distinguish them from naltrexone, which is a full opioid antagonist. **TABLE 12** and **TABLE 13** describe different characteristics of MAT drugs.

(TABLE 12)

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[338]

(TABLE 13)

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 potential 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[339]

b. The choice to initiate MAT medication should be made jointly with the patient. Unlike methadone, which requires a referral to a federally licensed program, buprenorphine can be dispensed in primary care settings. Even patients in acute withdrawal who desire MAT with methadone can be treated with buprenorphine in the ED; the medication can be continued until they have had the opportunity to enter an opioid treatment program (OTP). Patients can easily be transitioned from buprenorphine to methadone, but the reverse is more problematic because of the risk of precipitating withdrawal. Methadone can be administered hours after a patient has received buprenorphine; however, buprenorphine may need to be withheld for several days for patients who have been using licit or illicit methadone.
c. Patients must be in opioid withdrawal (clinical opioid withdrawal scale [COWS] ≥8) before receiving buprenorphine (Appendix VI). If patients are initiated on buprenorphine prematurely, they may experience severe precipitated withdrawal. Management of precipitated withdrawal usually involves dosing with additional buprenorphine and possibly adjunctive medications. Failing that, treatment of precipitated withdrawal with a full opioid agonist with strong affinity for the mu receptor may be appropriate. Some patients may have prior negative experience with precipitated withdrawal. A careful, collaborative history and clinical assessment decreases the risk of precipitated withdrawal.
d. Within the ED, all prescribing clinicians are able to order and administer buprenorphine. An X-waiver is only required to prescribe buprenorphine for home use.
e. Although the DEA has restricted the prescribing of buprenorphine to physicians who hold a special certification and waiver, there is an exception for emergency situations called the "three-day rule," which allows a clinician without an X-waiver to dispense the medication by adhering to certain guidelines. A physician may administer but not prescribe a daily dose of buprenorphine to relieve withdrawals and cravings for three consecutive days (72 hours). Hence, a patient with OUD can return to the ED to get buprenorphine as they are bridged to an addiction specialist. The use of high dose buprenorphine, as recommended in these guidelines and www.coloradomat.org, may negate the need for patients to return daily.
f. **APPENDIX VII**, Buprenorphine Hospital Quick Start, provides an algorithm for identifying and treating patients with buprenorphine.
g. Rocky Mountain Poison Center (RMPC) can provide guidance for initiation of buprenorphine for providers who are new to administering the drug or in difficult cases such as pregnancy or induction from methadone. RMPC can be reached at 888.211.7766. The emergency clinician should specify that the call is opioid-related.
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 the ED.
i. Treatment with buprenorphine or methadone significantly reduces all-cause mortality and opioid-related mortality and morbidity.[340,341]
j. Patients in untreated opioid withdrawal may experience autonomic dysregulation that exacerbates their condition and complicates their care.
k. Patients not interested in long-term MAT may still benefit from buprenorphine during their ED visit to reduce craving and withdrawal symptoms. In addition, patients who initially refuse MAT may be more receptive to treatment after their withdrawal symptoms are controlled.

4. **EDs are encouraged to establish MAT protocols that use a multidisciplinary team approach for the treatment of OUD. Colorado EDs are urged to adopt the algorithms and policies published on the ColoradoMAT website, www.coloradomat.org.**
   a. ColoradoMAT (www.coloradomat.org), an excellent MAT resource, was developed through a partnership with Colorado ACEP, CHA, Project Shout and RMPC.
   b. ColoradoMAT provides many well-developed algorithms and resources for building a MAT program in the ED. Some of these protocols are listed below, but additional resources are available on the website.
      i. Buprenorphine Hospital Quick Start — **APPENDIX VII**
      ii. Managing Acute Pain in Patients on MAT — **APPENDIX X**
      iii. The entire care team, including nurses and social workers, should be educated in MAT and engaged in providing care for patients with OUD. **TABLE 14** provides a checklist for starting a MAT program in the ED.

(TABLE 14)

Checklist for Starting a MAT Program in the ED

- ☐ Identify program champions.
- ☐ Engage key stakeholders, including hospital administration, pharmacy, nursing and social work.
- ☐ Develop separate protocols for the initiation of buprenorphine.
- ☐ Build order sets for ED prescribing.
- ☐ Put MAT agents in the hospital formulary.
- ☐ Conduct provider education.
- ☐ Develop patient education materials.
- ☐ Establish protocols for discharge.
- ☐ Develop relationships with local outpatient treatment programs to facilitate seamless follow-up protocols.
- ☐ Establish ongoing quality assessment for the ED MAT program.

SOURCE: Project SHOUT[339]

5. **Ideally, patients who present to the ED in opioid withdrawal, whether from OUD or cessation of long-term opioid medications, would receive symptomatic treatment – preferably with buprenorphine.**
   a. Opioid withdrawal is potentially life threatening. In an attempt to mitigate uncomfortable withdrawal symptoms, patients are more likely to inject a higher potency or greater amount than usual, increasing their risk of overdose and death.
   b. Although symptomatic management with nonopioid medications can relieve specific symptoms, it is unlikely to be completely effective and does little to prevent relapse.
   c. Buprenorphine is recommended for the treatment of uncomplicated opioid withdrawal. A flowchart can be found at www.coloradomat.org or in **APPENDIX VII**.

d. Buprenorphine or buprenorphine/naltrexone are preferred in the ED setting for the treatment of opioid withdrawal and initiation of MAT.
   i. Calculate the patient's COWS score before initiating buprenorphine **(APPENDIX VI)**. A score >8 is recommended prior to the initiation of buprenorphine.
   ii. Moderate to severe withdrawal symptoms are necessary; the premature administration of buprenorphine can worsen withdrawal symptoms (i.e., precipitated withdrawal).
   iii. Patients who present in mild withdrawal can be observed until symptoms become more significant. Although this approach is preferable to asking the patient to return, it may not be feasible in all situations due to time constraints.
   iv. Initiate buprenorphine 8 mg SL and observe the patient for one hour while monitoring for symptom improvement.
   v. If improvement is observed, provide an additional loading dose of 8-24 mg SL. Consider a higher loading dose if outpatient treatment may be delayed. The patient can then be successfully discharged without further observation.
   vi. If no improvement is noted, evaluate for other etiologies, buprenorphine side effects, incompletely treated withdrawal and the accidental precipitation of withdrawal. See **APPENDIX VII** for a more thorough discussion.

e. Clinical signs of withdrawal can vary based on the primary opioid used:
   i. >12 hours after short-acting opioids (e.g., oxycodone, hydrocodone, heroin)
   ii. 16-24 hours after long-acting opioids (i.e., sustained-release formulations)
   iii. 48-72 hours for methadone

f. For cases in which buprenorphine is inappropriate, withdrawal can be treated with alpha-2 agonists, antiemetics and NSAIDs. See **APPENDIX VIII**, Adjuvant Treatment of Opioid Withdrawal, for further descriptions.

6. If a patient is withdrawing from methadone, emergency clinicians are advised to consult with a toxicologist or addiction specialist prior to initiating treatment with buprenorphine to avoid the risk of precipitated withdrawal.

a. Methadone is a high-risk, tightly regulated drug with a very long half-life and unpredictable metabolism. The premature initiation of buprenorphine causes precipitated withdrawal.
b. A consultation with addiction medicine specialists or poison control is recommended prior to the administration of buprenorphine.
c. Rocky Mountain Poison Center, which can guide clinicians through the initiation of buprenorphine in difficult cases, can be reached at 888.211.7766. It is important to specify that the call is opioid-related.

7. Patients presenting to the ED in pain and already receiving MAT upon arrival to the ED should receive adequate analgesia with ALTOs and, if needed, opioid agonists.

a. Opioid-sparing ALTO modalities are recommended as the first-line treatment for all patients, including those on MAT. (See **APPENDIX X**, Managing Acute Pain in Patients on MAT, for further guidance.)
b. The use of MAT will often alter the management of acute pain in the ED. A patient's usual dose of buprenorphine or methadone will not provide adequate analgesia alone.
   i. In case of an extended stay in the ED or pending admission, splitting the patient's daily dose into three separate doses may provide additional analgesic benefits. The analgesic effects of both buprenorphine and methadone occur early in dosing and then wear off, so splitting doses may provide improved analgesia.[342,343]
c. Patients and clinicians may not always be able to differentiate between withdrawal symptoms and pain from other causes. The COWS scale may help make this distinction.

d. Opioids should not be withheld when ALTO pathways fail to adequately control pain simply because a patient is on buprenorphine or methadone. Patients taking opioid agonists will have a higher tolerance to opioids. The prevalence of opioid-induced hyperalgesia is unknown, but can complicate pain management for some opioid-dependent patients.
   i. Opioid-tolerant patients often require higher than typical doses of opioids.[344]

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

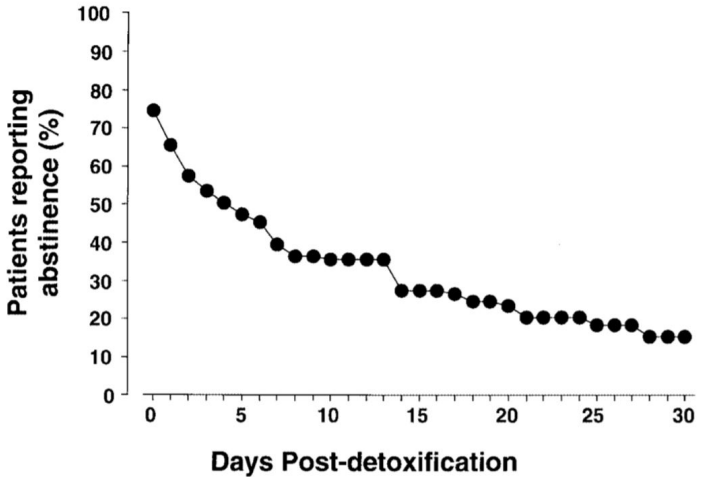
a. As a full opioid antagonist, naltrexone blocks the analgesic effects of most opioids. Naltrexone comes in two forms, an oral tablet usually used for the treatment of alcohol use disorders and a long-lasting monthly depo injection used for OUD.
b. Patients who have been on naltrexone and no longer have it in their system may have lower opioid tolerances than they did previously, so caution must be used.
c. Hold naltrexone upon presentation for acute pain that may require opioids.
d. If naltrexone is still present, pain management should center on ALTOs, including but not limited to NSAIDs, APAP, ketamine, local/regional anesthesia or conscious sedation with nonopioids as needed.
e. If naltrexone is still present and opioids are necessary, high-dose opioids can be used to out-compete naltrexone at the opioid receptor. The patient must be closely monitored, at minimum with pulse oximetry and telemetry, to prevent over-sedation and unintentional overdose.

9. "Detox" and abstinence-oriented therapies are ineffective for the treatment of OUD and are not recommended. It is imperative to counsel patients, families and caregivers on the ineffectiveness and risks associated with abstinence-oriented programs.

a. For patients with moderate to severe OUD, willpower is rarely sufficient to override the craving for opioids or endure the symptoms of opioid withdrawal.
b. Abstinence-oriented treatments are not only ineffective for the treatment of OUD, they also increase the risk of overdose in patients who relapse. Relapse rates are greater than 80% in those undergoing abstinence-based treatments.[345,346]
c. Patients who prefer to abstain can be advised to cautiously taper their opioid use over the course of several years. It is still unknown if cessation is an appropriate goal; several studies show relapse rates consistently greater than 50% (one month after buprenorphine maintenance therapy was discontinued).[347-349]

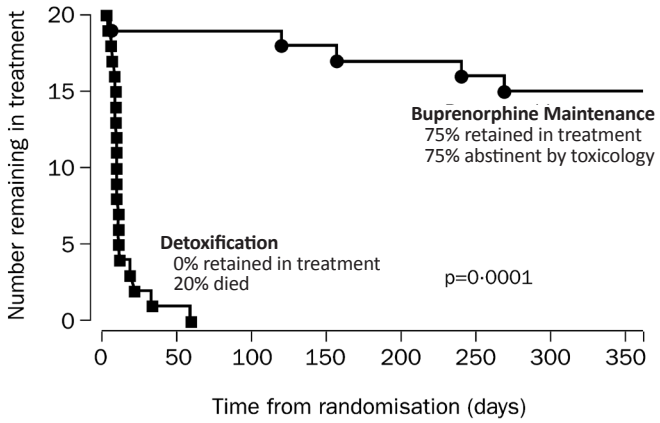
(FIGURE 10)

Inpatient Opioid Detoxification Outcomes (Heroin)[350]



(FIGURE 11)

One-Year Retention Detox vs Buprenorphine Maintenance[350]



d. One study of injection opioid users comparing detoxification versus buprenorphine maintenance highlights the potential harms of abstinence- and detoxification-related care versus MAT. None of the patients in the cohort who underwent abstinence-based therapy remained in treatment for more than 90 days and 20% died. Comparatively, 75% of patients who underwent MAT with buprenorphine were still in treatment at one year and no deaths were reported.[346]

e. Emergency physicians should discourage patients from pursuing an abstinence-based approach and counsel patients of the increased failure and overdose rates associated with such approaches. Emergency clinicians should discuss the evidence that MAT is more efficacious and work to address potential misconceptions or stigma around MAT.

10. EDs are encouraged to establish relationships with MAT providers to coordinate "warm handoffs" for patients initiated on MAT in the ED. This will improve chances of recovery and allow patients to continue care with outpatient MAT providers upon discharge.

a. Office-based opioid treatment (OBOT) programs can offer buprenorphine and naltrexone. These programs may be associated with addiction medicine specialists and embedded in other primary care and subspecialty outpatient practices.

b. OTPs, popularly known as methadone clinics, are highly structured, regulated facilities that administer methadone and buprenorphine daily on-site. OTPs may be a better option than OBOTs for patients who benefit from more structure and additional counseling support. These facilities are heavily regulated by the DEA, the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Colorado Office of Behavioral Health.

c. In most urban areas, there exist multiple options for both OBOTs and OTPs that can provide MAT. OpiRescue, a free mobile application and website (www.opirescue.com), 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 (www.findtreatment.samhsa.gov) provides a directory of MAT providers.

d. Naloxone should be directly distributed or prescribed to patients or caregivers in case of relapse or overdose.

e. **APPENDIX IX** provides a discharge checklist for emergency physicians and social workers that can aid in discharge planning.

Treatment of Opioid Use Disorder continued

11. **Emergency physicians are encouraged to strongly consider obtaining X-waivers to prescribe buprenorphine for patients with OUD. This is especially true for communities where outpatient MAT is difficult to access and may require further care coordination. Having an X-waiver allows emergency physicians 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. Any physician can order buprenorphine to be administered in the ED setting to treat acute opioid withdrawal.
    b. X-waiver training includes an eight-hour course for physicians (16 hours for advanced practice providers such as nurse practitioners [NPs] or physician assistants). The training provides valuable information about OUD, MAT and the management of special populations.
    c. X-waivers can be completed online and through various organizations; below are several that offer this service.
        i. IT MATTTRs – based in Colorado and has provided grant-based 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)
        iv. American Academy of Addiction Psychiatry (AAAP)

Policy Recommendations

1. **Increase local, state and federal funding for MAT services.**
    a. The treatment gap for OUD is unacceptably high. An adequate response to this public health crisis requires a substantial investment in a treatment system capable of serving the needs of all patients impacted by the opioid epidemic.

2. **Repeal the X-waiver requirement for prescribing buprenorphine.**
    a. It is not in the public's best interest to require a waiver for clinicians to treat patients with OUD, while no waiver is required to prescribe opioids.
    a. While more than 900,000 U.S. physicians are licensed to write prescriptions for opioids, fewer than 32,000 are authorized to prescribe buprenorphine for the treatment of opioid addiction.[351]
    b. The waiver requirement is a barrier to treatment and adds to the stigma surrounding OUD.
    c. Repeal of the X-waiver requirement is endorsed by ACEP, the American Academy of Emergency Medicine, the American Academy of Clinical Toxicology and ASAM.
    d. Similar deregulation has enabled the widespread use of buprenorphine in France and led to a 79% decline in opioid overdose deaths since 1995.[352]
    e. Legislation designed to eliminate the requirement for clinicians to obtain a DEA waiver to treat OUD with buprenorphine should be supported. Elimination of the waiver requirement will greatly aid efforts to close the treatment gap for OUD and reduce overdose deaths.

Treatment of Opioid Use Disorder continued

3. **Ease regulations around 42 CFR Part 2 to improve the sharing of critical health data.**
   a. 42 CFR Part 2 requires any patient with an SUD to provide explicit permission for an OTP or treating provider to share information about their medical care, even with other clinicians caring for the patient.
   b. 42 CFR provided an essential safeguard for privacy from 1975 until HIPAA was enacted in 1996. However, 42 CFR Part 2 has created two separate, poorly aligned systems of care that 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 primary care providers, specialists and hospital-based physicians are left unaware of a patient's maintenance on methadone. This proves dangerous when physicians prescribe QT-prolonging drugs, benzodiazepines or other medications that interact with methadone, resulting in potentially fatal drug interactions.
   d. The separation of SUD from the rest of medicine further stigmatizes a disease process that should be normalized.
   e. Colorado ACEP supports efforts to align 42 CFR Part 2 with HIPAA, while ensuring that patients' personal health information is not inappropriately shared with law enforcement agencies, health insurers, data clearinghouses, employers or other entities outside the patient-physician relationship.
   f. Colorado ACEP joins the AMA, the American Hospital Association, ASAM 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 directs the DEA to amend their rules regarding the face-to-face encounter required by the 2008 Ryan Haight Act when prescribing controlled substances.
   b. The Ryan Haight Act in effect eliminates the ability of clinicians to treat patients with OUD in rural areas, posing an unnecessary hindrance to care.
   c. The DEA is expected to release new rules soon that will allow the prescribing of buprenorphine via telemedicine without an initial face-to-face encounter.
   d. Colorado ACEP encourages a loosening of the act's restrictions to allow for telehealth prescription of buprenorphine in order to allow clinicians to better treat patients 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. The patient's ability to access proven medications like methadone and buprenorphine should never be conditional upon other treatment modalities. There are many other disease states that would benefit from psychosocial therapy in addition to medication management, but providers would never accept making one a requirement of 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 exist outside of OTPs within health care.

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. Select 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 OUD. 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 opioid usage, we can decrease the number of Coloradans who develop OUD 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 MAT 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—CHA, 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
SENIOR 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. Understanding Pain: A Complex Biopsychosocial Phenomenon
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
V. Screening Tools
VI. Clinical Opioid Withdrawal Scale
VII. Buprenorphine Hospital Quick Start
VIII. Adjuvant Treatment of Opioid Withdrawal
IX. Discharge Checklist for Patients Initiated on MAT
X. Managing Acute Pain in Patients on MAT
XI. Cannabinoids and Pain

Appendix I

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. Common sense and neuroscience agree that pain is not simply a process defined by receptors, neurological afferents and the interactions with the spinal cord and brainstem. Rather, it is an experience that integrates these biological elements with psychological and social conditions to produce the experience of pain.

To an extent not seen with other conditions, pain is a complex biopsychosocial interplay of peripheral and CNS processes that hinge on each patient's biology, psychology and social circumstances, which are intertwined and indivisible. Whether it is acute or chronic, easily treated or intractable, 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.

The Biology of Pain

Most physicians are aware of the distinctions between nociceptive pain (somatic or visceral), neuropathic pain, inflammatory pain and other less easily categorized types of pain (e.g., cancer pain, headache syndromes, fibromyalgia). Pain also differs in its duration, intensity, location and etiology. Sensorimotor pathways relay information about the nature of the pain stimulus. The cognitive and affective pathways evaluate and incorporate sensorimotor information, integrating it with information based on prior experiences and emotions.

Emergency physicians are encouraged to use opioid-sparing, multimodal analgesia as outlined in these guidelines, and to consult pain specialists for patients whose pain is not well managed. Regrettably, the indiscriminate prescription of opioids may have contributed to an epidemic of chronic pain. Opioid-induced hyperalgesia, a disorder that leads to the sensitization of pronociceptive mechanisms and a resultant decrease in the pain threshold, may contribute to persistent complaints.[353-355]

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 the significant genetic contributors and polymorphisms in pain tolerance and analgesic responsiveness.[356-358] Gender-based research, another important area of ongoing study, consistently demonstrates differences in pain threshold, susceptibility to chronic pain, and analgesia sensitivity between male and female patients.[359] Studies have also identified measurable electroencephalography signatures capable of predicting differences in pain tolerance between individuals.[360]

The Psychology of Pain

Neuroimaging studies demonstrate the significant extent to which cognitive and affective factors affect the experience of pain. The anticipation of pain and the patient's level of attention or distraction, mood, tendency to catastrophize and perceived level of control over their symptoms can modulate peripheral, spinal and central activity before, during and after a painful experience. The context of a painful stimulus and a person's prior life events further influence the way in which they experience pain.

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 an intensity of "x," she will experience pain. However, her prior positive interactions with dogs, the safe surroundings (home) and her certainty that the nip came from the puppy will modulate her negativity of the experience. The same woman, who has always been wary of the ocean, is now at the beach. After finally mustering the courage to wade in, she hears a lifeguard shout "Shark!" If she feels a nip at her ankles while in the water, she is likely to have a drastically different pain experience than she had with the puppy – even if the intensity of the two experiences is identical.

The anticipation of pain and expectations surrounding painful experiences, as well as 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, cognitive behavioral therapy, acceptance and commitment therapy, virtual reality therapy and mindfulness-oriented interventions that leverage insights into the cognitive and affective components of pain signaling.

The association between mental health, SUD and the experience of pain is well established.[184] The vicious cycle of pain begetting depression and anxiety, which then impairs patients' ability to effectively manage their symptoms, is familiar to most physicians. Functional neuroimaging demonstrates shared neural mechanisms for pain, depression and anxiety.[361-363]

Finally, it is important to acknowledge the critical role that physician empathy can play in promoting pain relief.[364] Because the psychology of patient-doctor interactions influences the way patients experience pain and analgesia, physician desensitization to pain complaints can undermine the quality of care and decrease the provider's professional satisfaction.[365] Physicians who become frustrated when treating a patient with intractable pain are advised to consult with pain medicine and mental health specialists.

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 these experiences.[366] Although pain is universally experienced, it is not universally understood. Patients, families and communities all value and understand pain differently. Furthermore, types of pain can be tempered by their social repercussions. Genital pain, for example, may be more isolating than back pain, as the former cannot easily be talked about with others. This ensuing isolation can intensify the pain experience. It is interesting to note that the brain activation sparked by social rejection or exclusion is very similar to that caused by physical pain. In an age of ever-widening income inequality and persistent racial disparities in health status, it is important to consider the measurable, complex impact that poverty and racism can have on pain perception.

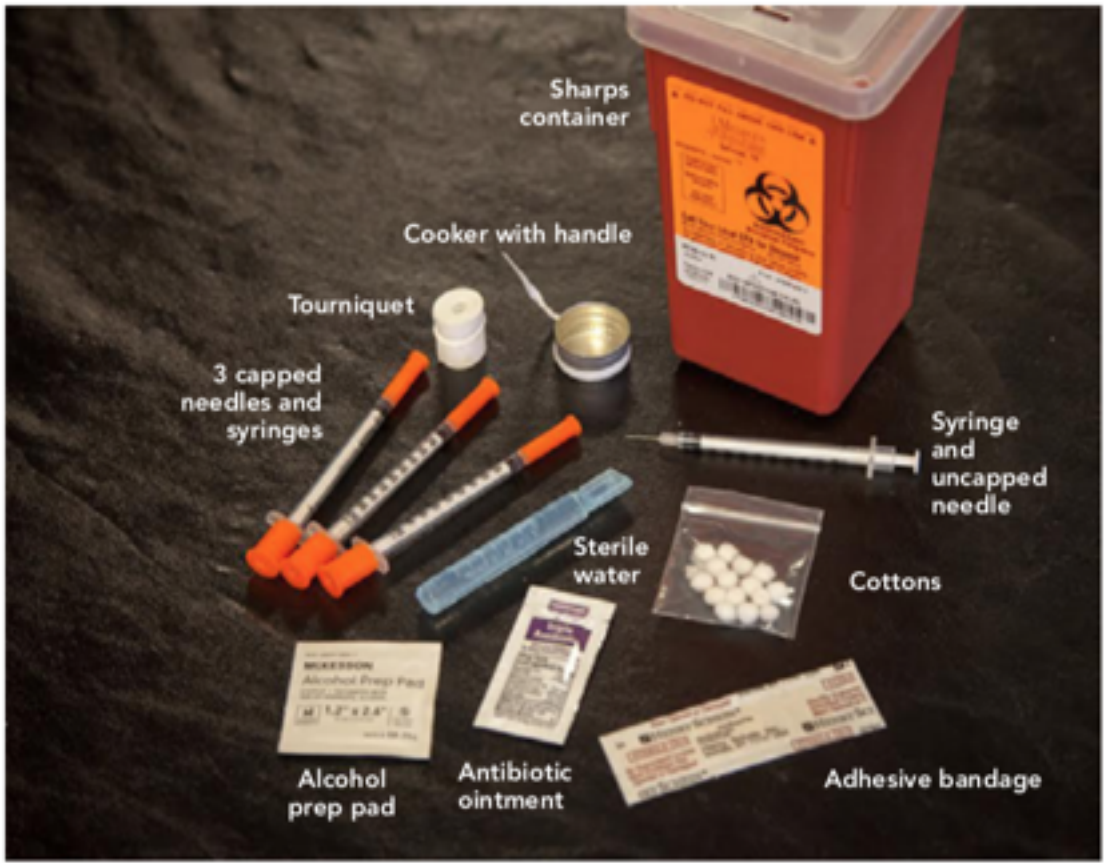
The Biopsychosocial Model of Pain: Implications for Clinicians

The biopsychosocial model of pain underscores the importance of valuing and addressing each of these components. While a review of the state of pain neuroscience is beyond the scope of these guidelines, functional neuroimaging suggests that 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, therefore, implicitly or explicitly 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" that gives rise to one unified pain experience.[367]

To an extent not seen with other conditions, the biology of pain is the sociopsychology of pain. It is vital for physicians to recognize that the experience of pain is distinct for every individual; as such, the psychological and social determinants of pain are just as real—and worthy of treatment – as any observable injury. Physicians serve their patients best when they involve pain specialists, mental health providers, physical therapy and social workers in the management of patients with complex pain presentations.

Appendix II

Materials Used for IV Drug Use



SOURCE: 2017 Colorado ACEP Opioid Prescribing & Treatment Guidelines[42]

Appendix III

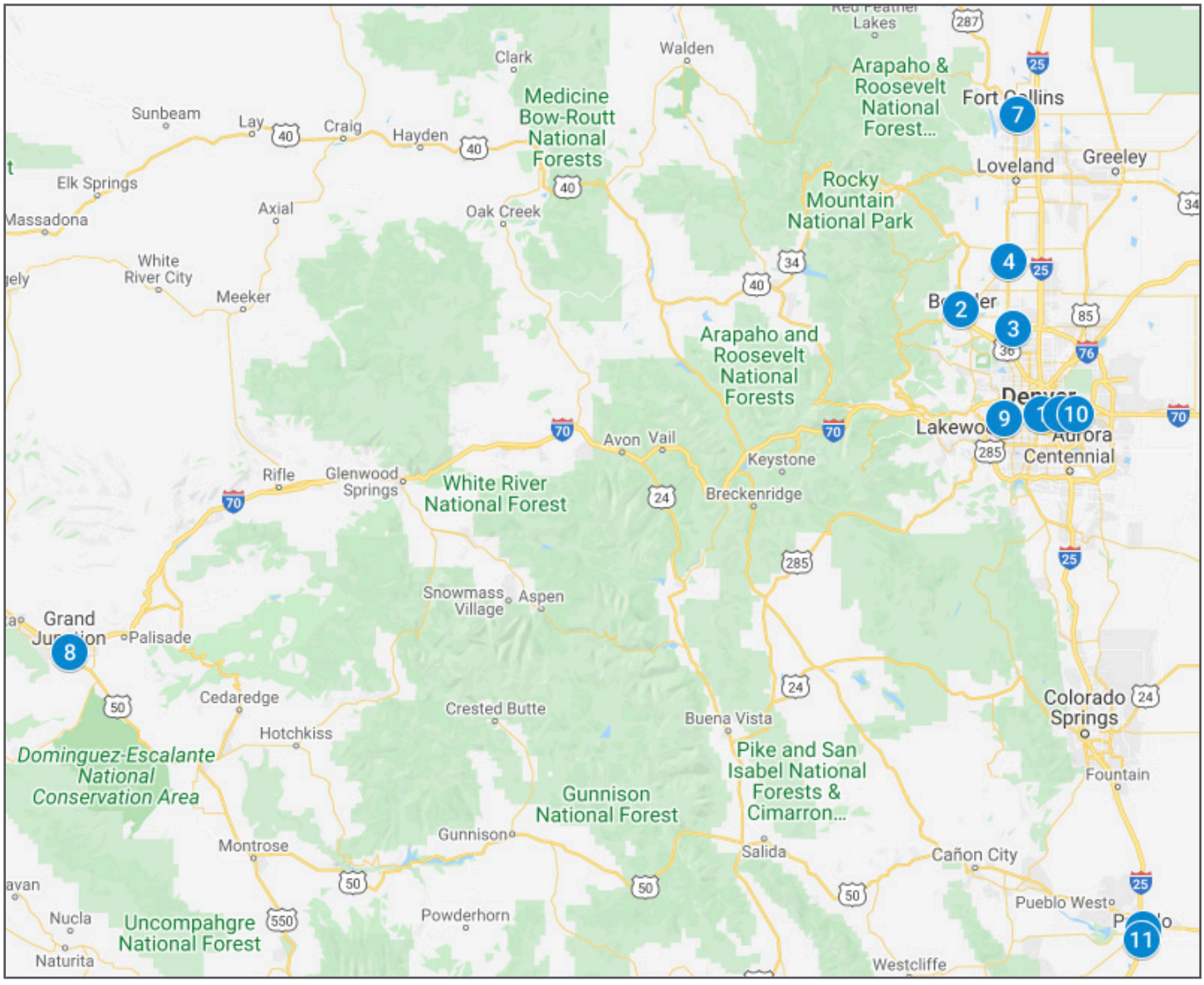
Steps to Injecting Heroin and Unsafe Practices

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	3482 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	Northern 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	Western 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

Colorado Department of Public Health & Environment keeps an updated list of SEPs which may be accessed at https://www.colorado.gov/pacific/cdphe/reducing-infections-injection-drug-use

Appendix V

Screening Tools

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

Opioid Risk Tool — OUD (ORT-OUD)

This tool should be administered to patients upon an initial visit prior to beginning or continuing opioid therapy for pain management. A score of 2 or lower indicates low risk for future opioid use disorder; a score of >/=3 indicates high risk for opioid use disorder.

Mark each box that applies:	Yes	No
FAMILY HISTORY OF SUBSTANCE ABUSE		
Alcohol	1	0
Illegal drugs	1	0
Rx drugs	1	0
PERSONAL HISTORY OF SUBSTANCE ABUSE		
Alcohol	1	0
Illegal drugs	1	0
Rx drugs	1	0
AGE BETWEEN 16-45 YEARS	1	0
PSYCHOLOGICAL DISEASE		
ADD, OCD, bipolar, schizoophrenia	1	0
Depression	1	0
SCORING TOTALS	____	____

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.

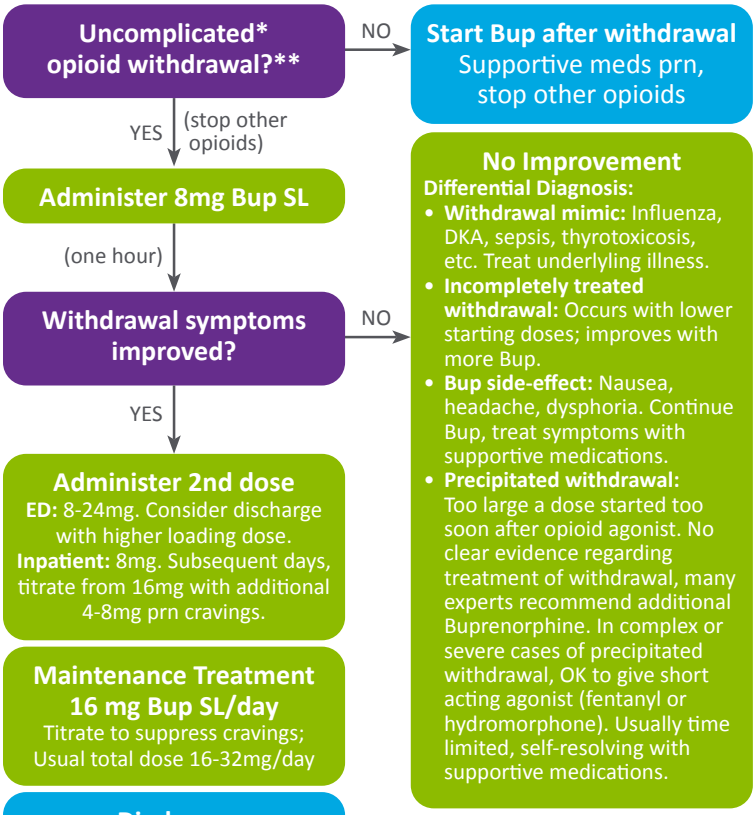
Initials of person completing assessment_____

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

Appendix VII

Buprenorphine Hospital Quick Start

- Any prescriber can order Bup in the hospital, even without an x-waiver.
- Bup is a high-affinity, partial agonist opioid that is safe and highly effective for treating opioid use disorder.
- If patient is stable on methadone or prefers methadone, recommend continuation of methadone as first-line treatment.



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.

SOURCE: www.ColoradoMAT.org

Appendix VIII

Adjuvant Treatment of Opioid Withdrawal

The treatment of choice for acute opioid withdrawal is buprenorphine or methadone. In the rare case that these medications are clinically contraindicated, emergency physicians can administer 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 is also encouraged as an adjunct to opioid-agonist therapy:

Alpha-2-Agonists

- Clonidine is effective for ameliorating withdrawal symptoms.[368] Typical regimens consist of 0.1-0.3 mg given orally in two to four doses per day (up to a maximum of 1.2 mg per 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).
- 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 per day for seven days; however, adverse effects are unpredictable due to the lack of titration.
- Lofexidine is an alpha-2-agonist approved by the FDA in 2018 for the treatment of opioid withdrawal. While lofexidine and clonidine are equally effective for the treatment of opioid withdrawal, lofexidine produces less hypotension.[368] Lofexidine, however, is significantly more expensive than clonidine.

Antiemetics

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

Anticholinergics

Medications such as dicyclomine may be given to alleviate abdominal cramping and pain.

Antihistamines

Hydroxyzine can be used for anxiety and dysphoria.

NSAIDs

Ibuprofen, naproxen and ketorolac can be used for headache, myalgias and pain.

Benzodiazepines (CAUTION)

These agents are generally not recommended, as their potential for abuse and side effects typically outweighs their benefits—patients must be strictly monitored.

Appendix IX

Discharge Checklist for Patients Initiated on MAT

For patients initiated on buprenorphine during their ED stay:

- ☐ Social workers and clinicians can call a local buprenorphine prescriber to arrange a "warm handoff" and schedule an appointment (ideally within three days) for the patient after discharge.
- ☐ Hospital providers with an X-waiver to prescribe buprenorphine can write a discharge prescription for buprenorphine or buprenorphine/naloxone to last until the patient's upcoming appointment.
- ☐ If no X-waivered provider is available, consider one of the following:
  a. Schedule a patient appointment with an X-waivered provider for the day after discharge.
  b. Advise the patient to return to the ED for the administration of buprenorphine. This is permitted for up to three days as a bridge to the first outpatient appointment.[369]
  c. Consider providing a loading dose up to 32 mg; this may prevent withdrawal for up to 72 hours without causing clinically significant sedation or respiratory depression.
- ☐ Dispense or prescribe naloxone.

Appendix X

Managing Acute Pain in Patients on MAT

1. The use of methadone, buprenorphine or naltrexone for the treatment of OUD may complicate pain management in the ED.
2. A patient's usual dose of buprenorphine or methadone generally does not provide adequate pain control. Analgesia should be offered to patients receiving MAT who are in pain.
3. The use of pharmacologic and procedural ALTOs should be maximized in patients receiving MAT. See ALTO Treatment Pathways (above) for the management of specific pain presentations.
    a. Splitting home doses of buprenorphine or methadone three times per day is sometimes sufficient for treating very mild acute pain. The analgesic effects of these medications last less than 24 hours, so doses must be split.[137,138]
    b. Clinicians are encouraged to use nonopioid medications as first-line agents and follow ALTO pathways. The following agents may be of particular value for the treatment of patients undergoing MAT:
        i. All patients in pain should receive scheduled APAP and an NSAID, except when clinically contraindicated.
        ii. Gabapentinoids: Gabapentin (300-600 mg PO three times per day) and pregabalin reduce pain and opioid consumption.
        iii. Alpha-2 agonists: Clonidine and dexmedetomidine are 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]).
        iv. Ketamine and magnesium: 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 as needed. In addition, magnesium is an NMDA receptor antagonist with analgesic and opioid-sparing effects (e.g., 30-50 mg/kg bolus followed by 10 mg/kg/hr).
        v. IV lidocaine: A bolus of 1-1.5 mg/kg is followed by 1.5-3 mg/kg/hr. Contraindications include cardiac dysrhythmias. Serum levels must be monitored after 24 hours.

Appendix X continued

4. The following medications may be useful adjuncts for treating the symptoms that accompany acute pain in patients receiving MAT:

a. Useful medication adjuncts

- Cyclobenzaprine 5 mg tabs or Tizanidine 2-4 mg every six hours as needed for muscle spasms
- Ondansetron 4 mg PO every six hours as needed for nausea
- Haloperidol 2.5-5 mg PO every six hours as needed for nausea or abdominal pain
- Dicyclomine 10-20 mg PO every six hours as needed for stomach cramping
- Lorazepam 0.5-1 mg PO every eight hours as needed for anxiety
- Antipsychotics as needed for psychotic disorder symptom control
- Nicotine replacement as needed for tobacco dependence

b. Consider use of regional and local anesthesia when possible (see ALTO Procedures above).

c. Consider consulting anesthesia or pain medicine for use of neuraxial or specialized regional anesthetic techniques in patients with severe pain not controlled with ALTO modalities.

d. If opioid analgesics are needed for adequate pain control, they can be given to patients on MAT. Due to cross-tolerance and increased pain sensitivity, higher than typical doses of opioids should be anticipated.

i. As with all patients receiving opioids, these patients should be monitored closely, and naloxone should be used if there is respiratory depression or severe over-sedation.

ii. For patients receiving buprenorphine for addiction treatment for whom ALTO modalities have failed, consider treating acute pain with additional buprenorphine doses.

1. There is no clinical ceiling on buprenorphine for analgesia. SL buprenorphine can be given as frequently as q2h. IV buprenorphine is a potent analgesic. Start at 0.3 mg IV and titrate as needed. At higher doses respiratory depression does occur, but has a ceiling effect of about 50% reduction in baseline.[370]
2. 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.

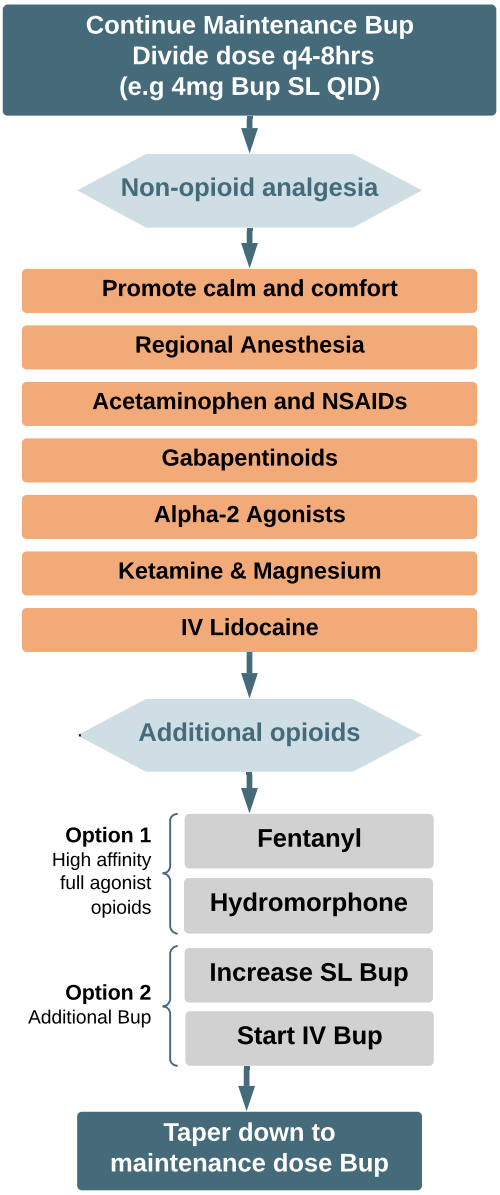
iii. As a full opioid antagonist, naltrexone will block the analgesic effects of most opioids. If naltrexone is still present and opioids are necessary, high dose opioids can be used to out-compete naltrexone at the opioid receptor. The patient must be closely monitored, at minimum with pulse oximetry and telemetry, to ensure that over-sedation and unintentional overdose does not occur.

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

CA BRIDGE
TREATMENT STARTS HERE

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

Emergency Department / Critical Care



Promote calm and comfort

Anxiety, fear, depression are common: Instill sense of control, provide education on self-management techniques such as mindfulness meditation. Reduce noise, uncertainty, confusion. Positioning, splinting, and physical comfort should be maximized. Minimize unnecessary NPO status.

TREAT UNPLEASANT SYMPTOMS:

Diphenhydramine 25-50mg PO q8h prn insomnia/anxiety
Tizanidine 2-4mg q6h prn muscle spasms
Ondansetron 4mg PO q6h prn nausea
Trazadone 50mg PO qhs prn insomnia
Melatonin 3mg PO qhs prn insomnia
Lorazepam 0.5-1mg PO prn anxiety
Antipsychotics prn psychotic disorder symptom control
Nicotine replacement prn tobacco dependence

Regional Anesthesia

Peripheral nerve blocks: superficial cervical plexus, brachial plexus, radial/median/ulnar, PECS, erratus plane, TAP, femoral, sciatic, posterior tibial.
Spinal and Epidural anesthesia

Acetaminophen and NSAIDs

Acetaminophen and **NSAIDs,** when not contrainidicated, should are the foundation of a multimodal analgesic strategy.

Gabapentinoids

In opioid depenent patients, the calcium channel inhibitors, gabapentin and pregabalin reduce postoperative pain and reduce opioid consumption. Gabapentin 300-600mg PO TID.

Alpha-2 agonists

Clonidine and Dexmedetomidine are anxiolytic and analgesic with significant opioid sparing affects. e.g. **Clonidine** 0.1-0.3mg PO q6-8h prn pain or anxiety (NTE 1.2mg/day, hold if BP <100/70).

Ketamine & Magnesium (NMDAR antagonists)

Ketamine is the most potent non-opioid analgesic for opioid tolerant patients. A brief infusion of 0.3mg/kg IV over 15min is followed by 0.3-1mg/kg/hr as needed.
Magnesium is also an NMDAR with analgesic and opioid sparing effect. eg. 30-50mg/kg bolus followed by 10-mg/kg/hr.

IV Lidocaine (Na channel antagonist)

Opioid sparing analgesic. A bolus of 1-1.5mg/kg is followed by 1.5-3 mg/kg/h. Contraindications include cardiac dysrthymias. Must monitor serum levels after 24hrs.

High Affinity Full agonist Opioids

Hydromorphone, fentnayl, and sufentanil can be added to maintenance Bup to provide synergistic analgesia. Titrate to analgesia and side effects. This will NOT cause withdrawal.

Additional Bup

There is no clinical ceiling on Bup analgesia. SL Bup can be given as frequently as q2h. IV Bup is a potent analgesic start at 0.3mg IV and titrate as needed. At higher doses respiratory depression does occur.

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 XI

Cannabinoids and Pain

Cannabinoids and Pain: Counseling Patients

1. Any patient with chronic pain should be encouraged to seek care from a pain medicine specialist.

2. As of this writing, no definitive, high-quality studies support the safety and efficacy of dispensary or pharmaceutical cannabinoids for analgesia. Until better evidence is available, physicians are discouraged from endorsing the use of cannabinoids for pain management.

3. Patients should be counseled that the use of any drug that lacks rigorous FDA drug development and safety profiles carries inherent risks.
   a. The testing and regulation of dispensary cannabis is poor to nonexistent.
   b. Products purchased at dispensaries are frequently mislabeled, contain undetermined content and may be contaminated with harmful substances.
   c. It is important to remind patients that cannabis dispensary workers are not trained to give medical advice.

4. Adverse effects associated with cannabinoid use include:
   a. The development of cannabis use disorder
      i. One in 10 cannabis users and one in six users under the age of 18 years will develop a cannabis use disorder.[371,372]
   b. Cannabis use disorders are associated with an increased likelihood of developing other SUDs.[373]
   c. Cognitive and behavioral:
      i. Short-term adverse effects include deficits in attention, memory and learning. Chronic use of cannabinoids may cause permanent cognitive deficits.[374,375]
      ii. 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.[410-419]
      iii. Cannabis use is associated with higher rates of depression,[376,420] anxiety[376] and suicidal ideation.[376,421]
   d. Cardiovascular:
      i. Smoking cannabinoids increases the risk for stroke and heart disease.[378-381]
   e. Pulmonary:
      i. Smoking cannabis can harm lung tissues, scar small blood vessels and expose patients to many of the same toxins, irritants and carcinogens found in tobacco smoke.[382,383]
      ii. Second-hand cannabis smoke is harmful to the health of exposed contacts, particularly children and adolescents.[384]
   f. Malignancy:
      i. Chronic cannabis use may increase the risk of testicular cancer.[385]
   g. Studies suggest that chronic use of cannabis may complicate pain management.[386,387]

5. Pregnant or breastfeeding patients are strongly advised to avoid cannabis use.

6. Despite the cautions above, medical providers may counsel their patients that many physicians, researchers, the AMA and the organizations represented in CO's CURE advocate for better scientific research into the safety and efficacy of cannabinoids for pain management.

Appendix XI continued

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 no risk of overdose death, their opioid-sparing potential and analgesic efficacy are unknown. 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.[388-390]

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.[391] Evidence regarding the efficacy of cannabinoids for the management of acute pain is nonexistent.[387] 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.[392-394]

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 THC and cannabidiol (CBD). The remaining cannabinoids and terpenes contribute to the smell, taste and possible pharmacologic effects of cannabis.[395] 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. 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."[396]

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.[392,393,397-400] The human endocannabinoid system is composed of the cannabinoid receptors CB1 and CB2 and the endogenous human cannabinoids anandamide and 2-arachidonoylglycerol.[401] 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 have immune system effect.[376,402]

Both cannabinoid receptors and endocannabinoids are involved in the regulation of pain sensation, with modulatory actions at all stages of pain processing pathways.[403] 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.[393] 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.[404,405] 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.[392-394]

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 NNT to achieve a reduction in pain was 24.[406] 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.[406] The number needed to harm (NNH), notably, was six. For comparison, the NNT for opioids is four and the NNH is five.[406]

The authors note that the change in pain intensity seen with cannabinoids was equivalent to a 3-mm greater reduction on a visual analogue scale when compared with placebo—well below the 30-mm threshold needed to represent a clinically significant difference.[406] 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.[406] 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.[406] The authors also 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, were not assessed by their review.[406] 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.[406]

These findings of the Stockings review closely mirror those of a 2018 Cochrane review 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.[407] A subsequent 2019 scoping review assessed data from 72 systematic reviews of medical cannabinoid use.[408] 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.[408] 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.[408] Until larger, more methodologically rigorous studies are conducted, the results of meta-analyses will be of limited value in guiding patients and providers.

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, suicidal ideation, 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.[409]

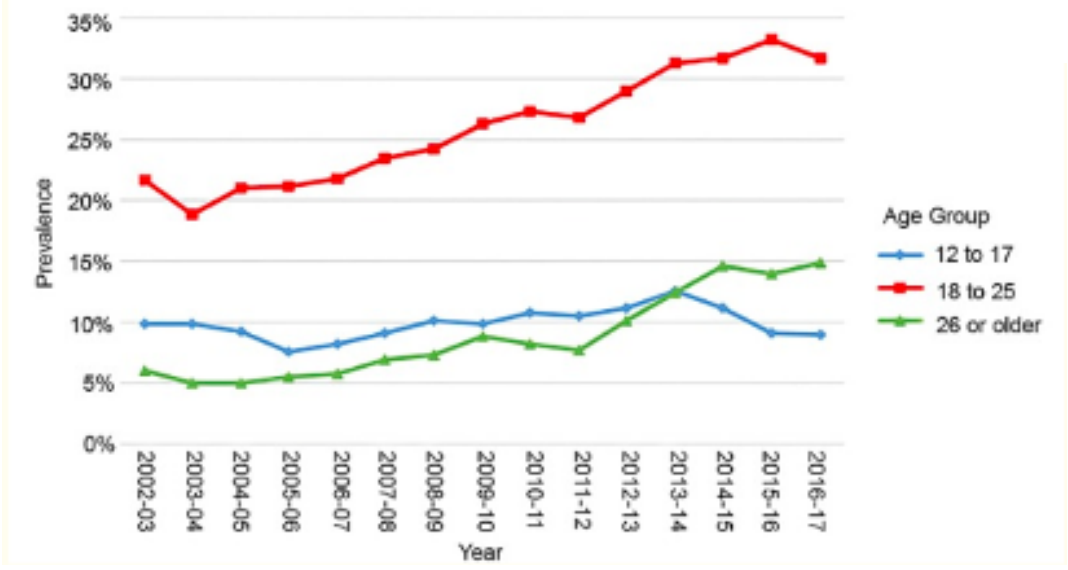
Appendix XIII continued

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,[410-419] depression,[376,420] anxiety[376] and suicidal ideation, attempts and completion.[421] A large prospective cohort study also linked cannabis use to a substantial risk for the later development of cannabis use disorder,[422] estimating that 9% of adults and 17% of adolescent users will develop the disorder.[371] Both grey- and white-matter changes have been found in chronic cannabis users, as have volume reductions in the amygdala and hippocampus.[423-427] 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 **(FIGURE 1)**. An estimated 39% of patients who receive chronic opioid therapy for pain report also using cannabis.[428,429] 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. Patients with chronic pain who inquire about cannabis for analgesia should be referred to a pain management specialist.

(FIGURE 1)

Cannabis Use In the Past Month In Colorado, by age group



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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