

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

Colorado Pharmacists Society

2020 Opioid Prescribing and Treatment Guidelines



*Developed by Colorado Pharmacists Society in partnership with Colorado Hospital Association,
Colorado Medical Society and Colorado Consortium for Prescription Drug Abuse Prevention*



COLORADO
MEDICAL SOCIETY



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Colorado Hospital Association

CO's CURE is a proud collaboration of the following sponsoring and participating societies and organizations. The CO's CURE initiative's leadership thanks each for its contributions, expertise and commitment to ending the opioid epidemic together.

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

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Table of Contents

Introduction 4

 The Origins of the Opioid Epidemic

 The Opioid Epidemic in Colorado

 CO’S CURE

Limiting Opioids in Clinical Practice..... 9

 Practice Recommendations

 Policy Recommendations

Alternatives to Opioids for the Treatment of Pain 19

 Practice Recommendations

 Policy Recommendations

Harm Reduction 28

 Practice Recommendations

 Policy Recommendations

Treatment of Opioid Use Disorder 34

 Practice Recommendations

 Policy Recommendations

The Future and Ending the Opioid Epidemic in Colorado..... 41

Appendices 42

 I. Additional Resources for Limiting Opioids

 II. Pharmacogenomic Guidance for Opioid Therapy

 III. Understanding Pain: A Complex Biopsychosocial Phenomenon

 IV. Links to National Society Pain Treatment Guidelines

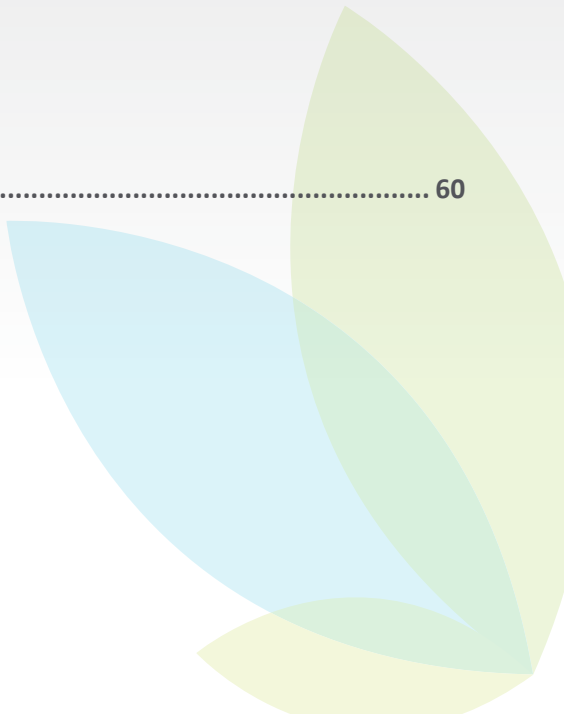
 V. Pharmacogenomic Guidance for Use of ALTO Agents

 VI. Cannabinoids and Pain

 VII. Additional Resources for OUD Assessment and Diagnosis

 VIII. Additional Resources for OUD Treatment

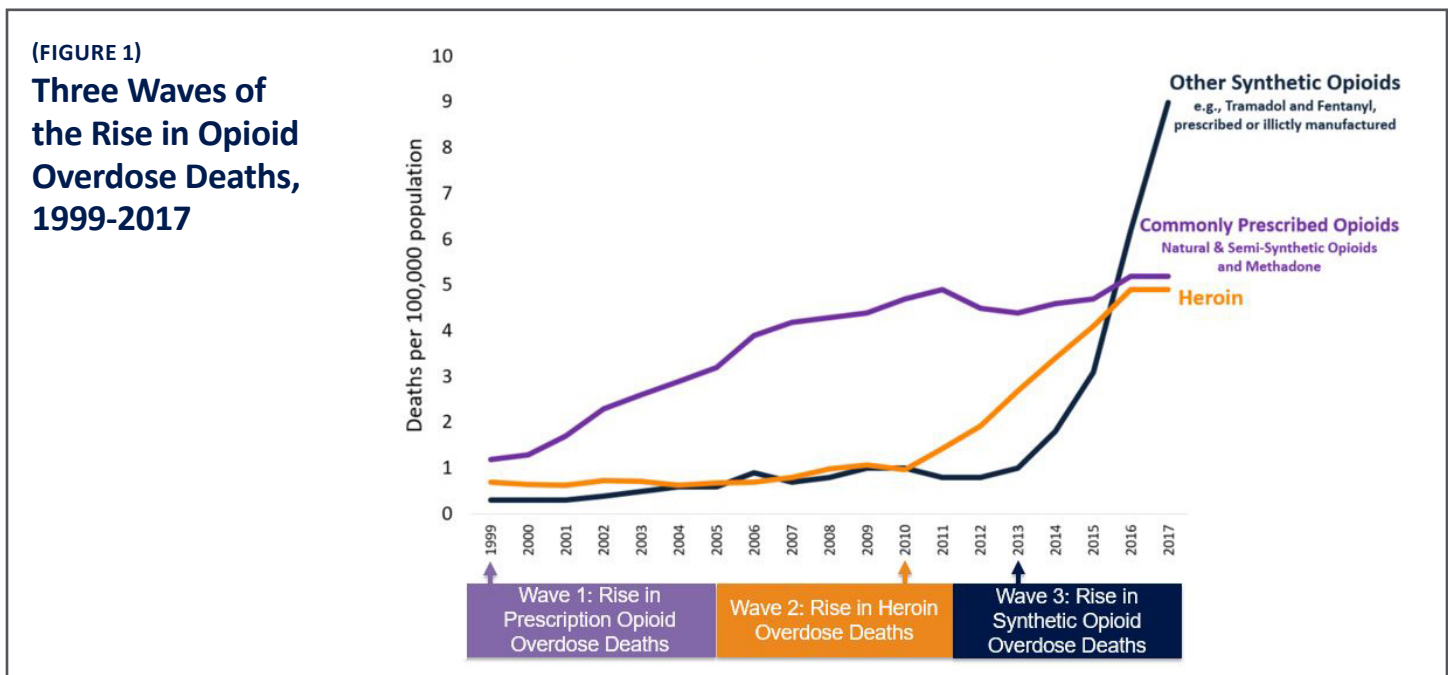
References 60



Introduction

Clinicians across Colorado and the nation are facing one of the most devastating public health crises in decades. Opioids, both prescription and illicit, have become the leading cause of accidental death in the United States for adults 50 years of age or younger.¹ Opioid-related adverse drug events (ORADEs), opioid overdose, physical dependence and the development of opioid use disorder (OUD) have become an increasingly common part of medical practice. The number of lives impacted by the crisis is astonishing. The Centers for Disease Control and

Prevention (CDC) reports that opioid overdose killed nearly 400,000 Americans between 1999 and 2017, and currently an average of 130 Americans die every day of opioid overdose (FIGURE 1).^{2,3} The economic costs of this epidemic are projected to exceed \$1.5 trillion by the end of 2020 (FIGURE 2); the human costs are incalculable.⁴ What makes this crisis especially tragic is that the medical establishment and the practice patterns of physicians have played a significant role in creating and perpetuating it.



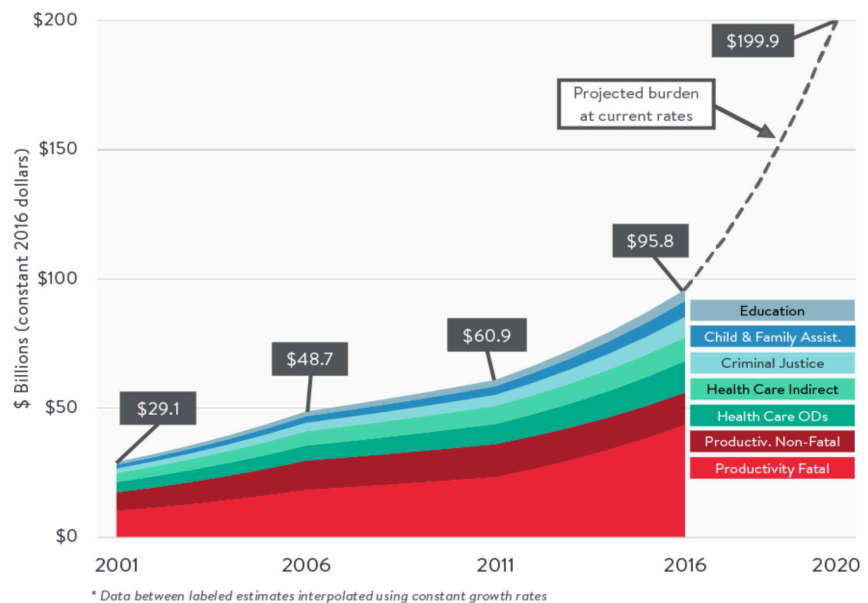
SOURCE: CDC MMWR²

More than 10.3 million people over the age of 12 years self-reported misusing opioids in 2018, with 9.9 million misusing prescription pain relievers and 808,000 using heroin.⁵ 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%).⁶ 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 over this time period. In 2017, there were 58 opioid prescriptions written for every 100 patients in the United States, with an average prescription length of 18 days.⁷

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 his or her first treatment admission is an average of seven years. For patients who die of an overdose, the time between their first exposure to an opioid and death is between nine and 13 years.^{8,9} In 2017, opioids were responsible for 34% of all substance use disorder (SUD) treatment admissions for patients aged 12 years and older.¹⁰ The economic implications of this epidemic are staggering. The nonmedical use of opioid pain relievers cost society approximately \$1 trillion between 2001 and 2016; unless major changes are made, the economic toll is projected to grow by another \$500 billion by the end of 2020 (FIGURE 2).⁴

Introduction continued

(FIGURE 2)
**Total and Projected Costs of
the Opioid Epidemic,
2001-2016**



SOURCE: Altarum⁴

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. Fortunately, clinicians, pharmacists and health care systems also have the power to reverse these grim statistics by reforming their practices with resolve and innovation.

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.¹¹ That changed in 1986, however, when pain expert Russell Portenoy published a limited case series of 38 hospital patients that suggested that chronic noncancer pain could be managed safely with high doses of opioids without posing a risk of addiction.¹² 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.¹³⁻¹⁶ 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.¹⁷ As a result, many pharmaceutical companies began to aggressively market their opioids for wider use at increased dosages and in extended-release formulations.

This shift in perspective was reinforced by the Veterans Health Administration, which adopted pain as the "fifth vital sign" in 1999.¹⁸ The Joint Commission, a governing body responsible for hospital accreditation, added pain management as a requirement for accreditation in 2000.^{2,11} 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."¹⁹ In addition to these mounting institutional pressures, patient satisfaction surveys increasingly compelled medical clinicians 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.^{2,20} Once reserved for the treatment of severe pain, opioid analgesics became routinely prescribed for a wide range of pain complaints.

Introduction continued

Further, the quantity and depth of pain and SUD education provided in health care education is concerning. In a survey of medical education, it was found that the mean number of hours dedicated to pain education is nine; however, some schools reported no pain education, and some reported five hours or less.²¹ In 1991, the American Association of Colleges of Pharmacy (AACP) stated that pharmaceutical education is responsible for preparing students to address substance use.²² However, a 2017 systemic review indicated limited hours of pharmacy education dedicated to SUD, with a majority of this time dedicated to smoking cessation.²³ While there is no data available regarding average hours of pain management taught, consensus recommendations from the Strategic Planning Summit for Pain and Palliative Care Pharmacy Practice suggest six 50-minute lectures (300 minutes) of essential content as required coursework.²⁴ Further research is needed to consider if pharmacy education is meeting this recommendation.

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, such as for end-of-life care and the treatment of pain associated with sickle cell disease, severe trauma, burns and cancer, it advocates using extreme caution in all cases. What follows is a compilation of ideas and suggestions that can be implemented by pharmacists and clinicians to aid in the prevention of opioid misuse and addiction and in the identification, treatment and support of patients with OUD. It is unlikely that a health system or pharmacist can or will attempt to implement each strategy or idea included in these guidelines. Rather, pharmacists and clinicians are encouraged to consider which of these suggestions are appropriate given their unique processes and resources. The recommendations in these guidelines are not intended to be a substitute for the oversight of legal counsel and compliance leaders.

The Opioid Epidemic in Colorado

Coloradans have been significantly affected by this national public health crisis. Since 2000, Colorado has seen 6,030 overdose deaths from opioids.²⁵ There were a total of 1,635 prescription opioid-related overdose deaths in the state from 2013 to 2017, which translates to 5.8 deaths per 100,000 residents. Heroin-related opioid overdose deaths have increased 76% since 2017.²⁶

Colorado Statistics

In 2017 in the state of Colorado:

- There were over 3.7 million opioid prescriptions dispensed to one million patients at retail (**TABLE 1**). These numbers fell slightly from a high of 4.3 million opioid prescriptions for 1.1 million patients in 2015.²⁶
- There were 1,012 drug overdose deaths, 57% of which involved an opioid.²⁶
- Fifteen percent of opioid-naïve patients were prescribed long-acting opioids.²⁷
- Ten percent of patient prescription days involved overlapping opioid and benzodiazepine prescription use.²⁷
- There were 671.3 opioid prescriptions filled per 1,000 residents.²⁷
- There were 134.3 treatment admissions for heroin per 100,000 people and 40.6 treatment admissions for pharmaceutical opioids per 100,000 people.¹

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

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 Profile²⁶

(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-naïve (%)	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

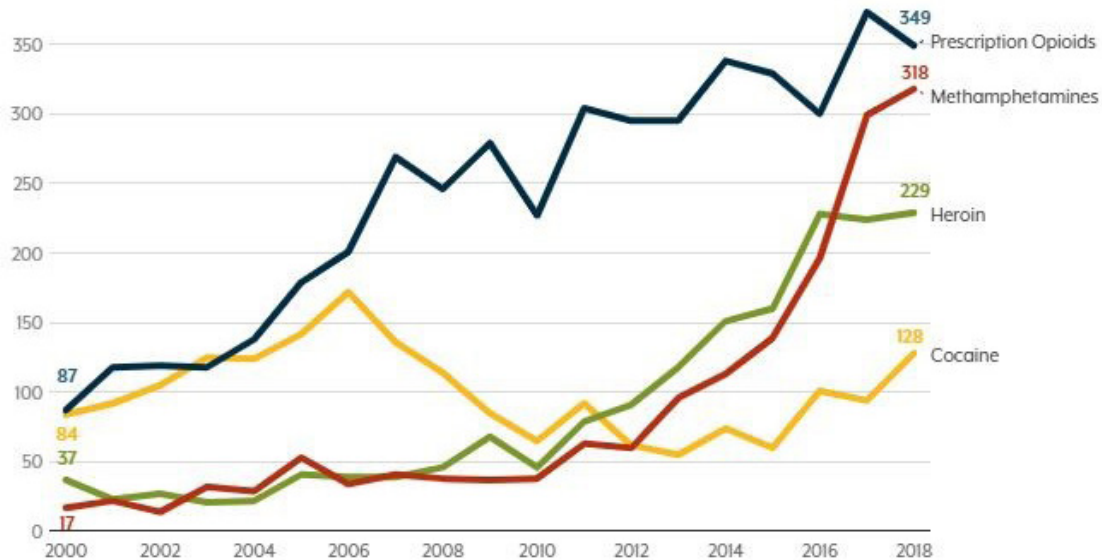
*Schedule II-IV Controlled Substances
Excludes Buprenorphine drugs commonly used for treatment
Annual percentages are based on average of quarterly percentages
Data Source: Vital Statistics Program, CDPHE and the Colorado Prescription Drug Monitoring Program, DORA
Data Analysis by: CDPHE, 2018*

SOURCE: Colorado Opioid Profile²⁶

Introduction continued

(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 Institute²⁸

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. Within each specialty, there is room for specific nuances of practices, and across all CO's CURE guidelines there is multispecialty collaboration with input from content experts. 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 implemented in Colorado emergency departments in

2017 through the Colorado Opioid Safety Pilot and later the Colorado ALTO Project, which were led by Colorado Hospital Association. The Colorado Opioid Safety Pilot resulted in a 36% decrease in opioid use as well as a 31% increase in the use of ALTOs for pain management in 10 pilot EDs over the six-month study period.²⁹ The success experienced in Colorado emergency departments through those initiatives represents just one front of efforts to confront the opioid epidemic in Colorado. To fully resolve the opioid epidemic, Colorado health care providers will need to adopt a more inclusive, coordinated and ambitious approach.

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



Limiting Opioids in Clinical Practice

Limiting Opioids in Clinical Practice

The vast majority of people who become addicted to opioids, both prescription and illicit, received their first dose by a provider's prescription.³⁰ This action inherently involves dispensing of the opioid by a pharmacist, placing responsibility on multiple health care professions. Across all specialties, a commonsense first step to addressing the epidemic of OUD is to decrease the frequency and ease with which opioids are prescribed and dispensed to patients with little or no previous exposure.

By virtue of their frequent contact with patients, pharmacists are uniquely positioned to support efforts to limit opioid use; indeed, patients visit their pharmacies 1.5 to 10 times more often than they visit primary care settings.³¹ These frequent patient contacts provide important opportunities for pharmacists to educate patients about their medications and to verify safe and appropriate use. As stated by the American Pharmacists Association (APhA), "Pharmacists receiving controlled substance prescription orders used for analgesia have a responsibility to ensure that the medication has been prescribed for a legitimate medical use and that patients achieve the intended therapeutic outcomes."³² The importance of the role pharmacists play in assessing and mitigating risk cannot be understated. The Colorado Pharmacists Society (CPS) recommends the following strategies to limit the use of opioids and optimize safe medication practices.

Practice Recommendations

1. Opioids are dangerous drugs with significant potential for misuse and addiction, numerous side effects, rapid development of tolerance, debilitating withdrawal symptoms and lethality in overdose. It is advised that they be avoided whenever possible and, in most cases, initiated only after other modalities of pain control have been trialed.

- a. Opioids are among the three broad categories of medications with potential for misuse, dependence and addiction, the other two being central nervous system (CNS) depressants and stimulants. Opioids act by attaching to opioid receptors on nerve cells in the brain, spinal cord, gastrointestinal (GI) tract and other organs, triggering a spike in dopamine that not only reduces the perception of pain but can also manufacture a powerful sense of well-being and pleasure by affecting the brain's limbic reward system.
- b. When used repeatedly, opioids induce tolerance, as exposure to opioids leads to loss of receptor activity and higher doses are required over time to produce the same effect.^{33,34} This mechanism also contributes to the high risk of overdose following a period of abstinence.³⁵ Tolerance can be lost in times of abstinence and exposure to a previously "safe" dose can lead to disastrous results.³⁶
- c. The effects of opioids are mediated by specific subtype opioid receptors (mu, delta and kappa) that are also activated by endogenous endorphins and enkephalins. The production of endogenous opioids is inhibited by the repeated administration of outside opioids, which accounts for the discomfort that ensues when the drugs are discontinued.
- d. Opioid therapy is associated with a number of common, sometimes serious side effects including sedation, respiratory depression, constipation, nausea and vomiting (TABLE 3).³⁷ These complications, which often necessitate additional medical care, can prevent patients from performing daily tasks and remaining active in the workforce.
- e. Genetic variation, particularly in the cytochrome P450 2D6 (CYP2D6) enzyme, creates significant patient variability in the metabolism of many opioids.³⁸⁻⁴⁰ This variability leads to increased rates of ORADEs for some patients and undertreatment of pain for others.
- f. Due to significant variation of individual genetic polymorphisms (specifically at CYP2D6), drug interactions and lowering of the seizure threshold, the routine use of tramadol when an opioid is warranted is not recommended.^{41,42}
- g. Due to its better safety profile, lower risk of abuse and decreased incidence of withdrawal, tapentadol may be considered over conventional opioids in certain patients when an opioid is warranted.⁴³⁻⁴⁶

Limiting Opioids in Clinical Practice continued

- h. Opioid-induced hyperalgesia (OIH) is a paradoxical phenomenon of increased sensitivity to noxious stimuli associated with long-term opioid use. Evidence suggests that even short-term exposures to opioids, particularly to potent agents like remifentanyl, may produce OIH.^{47,48}

i. Opioids can impair immune responses, promote angiogenesis and impact NK and T-cell function. In vitro, animal and some human studies suggest a possible association between perioperative opioid use and inferior oncologic outcomes. Research is ongoing to further understand this association.⁴⁹⁻⁵¹
- j. The risk-to-benefit ratio does not support the use of opioids if viable alternatives are available. Nonopioid analgesics, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), may be as effective as or more effective than opioids for the management of pain associated with some conditions.⁵²⁻⁵⁵

k. Additional resources regarding opioid pharmacology can be found within the APhA Opioid Use and Misuse Resource Center, found in **APPENDIX I**.

(TABLE 3)
Adverse Effects of Opioids

Common Side Effects	Serious Side Effect of Chronic Opioid Use
<ul style="list-style-type: none">• Nausea/vomiting• Constipation• Pruritus• Euphoria• Respiratory depression, particularly with the simultaneous use of alcohol, benzodiazepines, antihistamines, muscle relaxants or barbiturates• Lightheadedness• Dry mouth	<ul style="list-style-type: none">• 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.

Limiting Opioids in Clinical Practice continued

2. Pharmacists are encouraged to be familiar with and apply the principles of the Colorado Department of Regulatory Agencies (DORA)⁵⁶ and CDC guidelines for safe opioid prescribing,⁵⁷ treatment of acute pain, treatment of chronic pain and dispensing opioids.

a. Colorado DORA Guidelines for Prescribing and Dispensing Opioids

Last updated in 2019, these guidelines have been endorsed and supported by a variety of health care professions in Colorado, including the State Board of Pharmacy. These guidelines support use of the following strategies to limit opioid use:

- i. Before filling prescriptions for long-acting opioids and/or greater than 50 morphine milligram equivalents (MME), confirm that the patient's condition warrants the formulation, dosage and duration of opioids prescribed and that potential benefit outweighs risk.
- ii. When writing or filling prescriptions for long-acting agents, review for clinically relevant drug interactions, including interactions with CNS depressants (e.g., benzodiazepines, gabapentinoids, barbiturates, skeletal muscle relaxants, hypnotics, anticholinergic agents).
- iii. When filling prescriptions for long-acting agents, ensure the patient has received a short-acting agent for at least one week prior to adding or transitioning to a long-acting agent.
- iv. Ensure risk mitigation strategies are in place when warranted, through collaboration with the prescriber. Examples include naloxone prescription availability, monitoring and treatment agreements and pain management specialist referral if indicated.
- v. Collaborate with the health care team on a patient-specific pain management plan.
- vi. Provide education for patients and caregivers to determine a comprehensive pain management plan, including risk of opioid treatment and benefits of all pain management options.
- vii. Establish a plan with the patient for reducing/stopping opioid therapy when possible based on achievement of functional goals.

b. CDC Guideline for Prescribing Opioids for Chronic Pain

These guidelines were developed to improve the way opioids are prescribed, helping to ensure patients have access to safer, more effective chronic pain treatment while reducing the risks of OUD, overdose and death. Of the CDC's 12 primary recommendations, the following seven directives aimed at reducing inappropriate use and prescription of opioids are particularly relevant to pharmacist practice:

- i. Use immediate-release opioids at the outset of opioid therapy instead of extended-release/long-acting opioids.
- ii. Always use the lowest effective dose. Reassess evidence of individual benefits and risks when considering increasing dosage to greater than 50 MME/day, and avoid increasing dosage to greater than 90 MME/day whenever possible.
- iii. For acute pain, three days or less will often be sufficient; more than seven days will rarely be needed.
- iv. In conjunction with patients, set realistic goals for pain and function, and consider how opioid therapy will be discontinued if benefits do not outweigh risks.
- v. Evaluate benefits and harms with patients within one to four weeks of starting opioid therapy for chronic pain or of dose escalation. Evaluate benefits and harms of continued therapy with patients every three months or more frequently.
- vi. Only continue opioid therapy if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
- vii. Work with providers and patients to taper opioids to lower dosages or to taper and discontinue opioids.

Limiting Opioids in Clinical Practice continued

3. When patients are being initiated on or transitioned to a different opioid therapy, pharmacists are encouraged to assist prescribers in understanding relative potency of different medications and to use an opioid equivalency table or calculator.

- a. Most of the errors associated with preventable adverse drug events in hospitals occur at the ordering stage.⁵⁸
- b. Clinicians may be unaware of the relative potencies of different opioids and their morphine-equivalent dose; such oversights can lead to inadvertent overdose.
- c. Pharmacists can assist prescribing clinicians in calculation of starting doses, conversion between opioids using opioid equivalency tables and management of different routes of administration.
- d. When changing from one opioid to another, pharmacists may advise clinicians to reduce the dose of the new opioid by at least 25-50% of the calculated equianalgesic dose to account for interindividual variability in the response to opioids as well as the possibility of incomplete cross-tolerance.
- e. Pharmacists may be particularly helpful to clinicians in guiding decisions and calculations when converting to and from methadone, as well as to and from the atypical opioid agents (i.e., buprenorphine, tapentadol).⁵⁹

4. Pharmacists are encouraged to understand and recommend appropriate use of pharmacogenomic testing to optimize outcomes of opioid therapy and reduce adverse effects and risk of overdose.

- a. While there are many commercial pharmacogenomic tests marketed, not all genes tested on the list currently have strong evidence or are clinically actionable to guide opioid prescribing. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) have published peer-reviewed, evidence-based pharmacogenomic guidelines for CYP2D6 and opioids.^{39,60}

- b. Genetic polymorphism in CYP2D6 results in four metabolizer phenotypes: ultra-rapid (UM), normal (NM), intermediate (IM) and poor metabolizers (PM).^{38-40,61}
 - i. The hepatic CYP2D6 enzyme activates prodrugs like codeine to morphine and tramadol to O-desmethyltramadol; these metabolites have higher affinity for the μ -opioid receptor than the parent compounds.
 - ii. CYP2D6 also converts oxycodone to oxymorphone and hydrocodone to hydromorphone, with both the parent drugs and metabolites acting as μ -receptor agonists, but the metabolites have greater μ -receptor affinity.
- c. Patients who are CYP2D6-UM metabolizers have an increased incidence of adverse effects such as respiratory depression and nausea, while patients who are CYP2D6-PM may experience poor analgesic response to codeine and tramadol. Guidelines recommend avoiding hydrocodone and oxycodone in CYP2D6-UM and PM and using alternative nonopioid analgesics or opioids not metabolized by CYP2D6.^{38-40,61}
- d. The lack of reimbursement for pharmacogenomic testing is a barrier to wider use. Select patients who may benefit from genotyping include patients with a history of unusual opioid intolerances and those with uncontrolled pain despite adequate trial of opioid therapy.^{38-40,61}
- e. Pharmacogenomic results are used in context with other patient clinical factors (e.g., drug-drug interaction, renal function) to guide therapeutic decisions. One notable drug-drug-gene interaction involving CYP2D6-metabolized opioids is CYP2D6 inhibitors. Strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine) have been shown to phenoconvert CYP2D6 non-PM to behave like CYP2D6 PM phenotype and thus affect the efficacy of CYP2D6-metabolized opioids.^{38-40,61}
- f. See **APPENDIX II, PHARMACOGENOMIC GUIDANCE FOR OPIOID THERAPY.**

Limiting Opioids in Clinical Practice continued

5. Pharmacists are encouraged to consult the Colorado Prescription Drug Monitoring Program (PDMP) with each fill of an opioid prescription to assess for potential drug interactions and information suggestive of possible misuse or diversion of controlled substances.

a. The Colorado PDMP is a useful tool to help both prescribers and dispensers identify possible aberrant prescription drug use and/or diversion.

b. Information available on the PDMP helps practitioners make better-informed decisions when prescribing and dispensing controlled substances to a patient.

c. APhA supports the establishment of a standardized and integrated nationwide PDMP that includes all federal, state and territory databases. APhA supports mandatory PDMP enrollment by all health care providers, mandatory reporting by all those who dispense controlled substances and appropriate system query by registrants during the patient care process related to controlled substances.³²

d. Review of information contained on a patient’s PDMP profile allows practitioners to determine if a patient is receiving prescriptions for controlled substances from multiple prescribers and if the patient is using multiple pharmacies. Ideally, patients will receive opioid medications from one pharmacy and one prescriber, particularly when receiving chronic opioid therapy (COT). Additionally, the PDMP identifies use of nonopioid controlled substances that would be concerning when used in combination with opioids, such as benzodiazepines.

e. In cases where the PDMP demonstrates potential opioid or prescription misuse (TABLE 4), a pharmacist is encouraged to call the prescribing clinician and to weigh benefits and risk of dispensing an opioid.
- (TABLE 4)
Indicators of Potential Misuse or Diversion⁶²
1. Frequent requests for early refills

2. PDMP shows use of many pharmacies or prescribers of controlled substances and/or frequent use of the ED for pain medications

3. Patient lives far from the prescriber and/or pharmacy

4. Patient chooses to pay in cash and will not use insurance coverage

5. Patients travel in groups, all with similar prescriptions for controlled substances from the same prescriber

6. Handwritten prescription presented at the pharmacy that appears altered or flawlessly thorough

7. The prescriber’s Drug Enforcement Administration (DEA) registration is currently suspended or pending suspension or revocation

8. Patient traveled to a pharmacy, and the pharmacist knows or reasonably believes another pharmacy refused to fill the prescription

9. Patient pressures the pharmacist to dispense the controlled substances through implied or direct threats

10. Patient appears to be intoxicated or exhibiting withdrawal symptoms

11. Patient presents with controlled and non-controlled substance prescriptions but requests only the controlled substance be filled (e.g., antibiotic and opioid)

12. Patient presents prescriptions for highly abused “cocktails” of controlled substance (e.g., a benzodiazepine in combination with an opioid, muscle relaxant and/or stimulant)

13. Prescription is for an unusual quantity and/or very high dose

14. Patient indicates the medication will be diverted
- Page 13

Limiting Opioids in Clinical Practice continued

6. When concerns exist for potential misuse, OUD or diversion, it is recommended that pharmacists refuse to fill opioid prescriptions and call the prescriber to relay those concerns.

- a. Under the Code of Federal Regulations, pharmacists have a “corresponding responsibility” to make sure that a prescription has been issued for a legitimate medical purpose by a prescriber acting in the usual course of professional practice.⁶³ As parties to this corresponding responsibility, pharmacists have the right to refuse dispensing a medication when patient safety is a concern.

- b. The College of Psychiatric and Neurologic Pharmacists (CPNP) developed guidelines titled *Opioid Use Disorders: Interventions for Community Pharmacists*, which provide guidance through the three-step process used to screen opioid prescriptions for safe use. This process can also be applied to other controlled substances. Table 5 is based on the recommended process from CPNP with minor modifications.⁶⁴

Limiting Opioids in Clinical Practice continued

(TABLE 5)

Three-Step Process for Screening Opioid Prescriptions for Safe Use

Step 1: Verify the prescription (receiving the prescription)

It is advised that the content of the controlled substance prescription meets state and federal requirements, that the prescription is within the prescriber's scope of practice and that the identity of the individual presenting the prescription (including confirmation of birth date and address) is verified.

Step 2: Assess the patient (process the prescription)

Pharmacists are encouraged to discuss medication indication, previous medication trials and current state of their medical condition with the patient. Pharmacists are advised to evaluate safety and appropriateness of the prescription through information collected in the patient's medical history, pharmacy profile review and from the PDMP. Through this review, pharmacists are screening for potential misuse or diversion. **TABLE 4** includes examples of "red flags" – indicators of potential misuse or diversion.

1. Pharmacists are advised to consider comorbid health conditions and exercise caution when dispensing opioids to those at increased risk for adverse drug reactions and accidental overdose. The following are examples of comorbidities and factors that increase risk of ORADEs:
 - a. Age > 60 years
 - b. BMI > 30 kg/m²; obesity hypoventilation syndrome
 - c. Cardiac comorbidities (i.e., congestive heart failure)
 - d. Current or past SUD
 - e. Current or past tobacco use
 - f. Organ dysfunction (e.g., renal or hepatic)
 - g. Pulmonary comorbidities (i.e., chronic obstructive pulmonary disease, obstructive or central sleep apnea, use of supplemental oxygen)
 - h. Use of other sedating agents
2. It is recommended that pharmacists conduct a reasonable inquiry into concerns that arise regarding potential misuse, addiction or diversion and that the steps taken to inquire into the concern be documented.
 - a. If concerns are identified, it is recommended to first have a conversation with the patient:
 - i. It is advised to use open-ended questions to discuss how the patient is taking their medication, how well it works for their pain and nonpharmacologic methods tried.
 - ii. Does the patient need assistance navigating insurance issues? Is a therapy change warranted due to inadequate pain control?
 - iii. If concerns remain after discussion with the patient, contact with the prescriber is recommended to ensure opioid prescriptions are for a legitimate medical purpose and within the scope of the prescriber's practice. Pharmacists may discuss the potential need for a therapeutic modification, if deemed clinically necessary.
 - b. If concerns are not resolved after discussion with the patient and prescriber and/or if the prescription is presumed fraudulent, the following steps are recommended:
 - i. Discuss with the patient that the pharmacist cannot fill this prescription.
 - ii. If there are concerns but the prescription is legitimate, return the prescription to the patient.
 - iii. If it is known that the prescription is fraudulent, confiscate the prescription. Notify the patient's primary care provider, the provider of record on the fraudulent prescription and, when applicable, local law enforcement and regulatory agencies.
 - c. Pharmacists are encouraged to discuss concern regarding SUD with the patient.
 - i. It is recognized that this is a challenging discussion. Consider choosing a private, quiet location to discuss history.
 - ii. Screening, Brief Intervention, and Referral to Treatment (SBIRT) is a strategy that can help pharmacists identify patients with untreated OUD. **APPENDIX I** provides additional resources related to SBIRT and motivational interviewing training options.
 - iii. When appropriate, it is suggested that pharmacists refer patients for further follow-up or treatment for potential OUD (e.g., rehabilitative care centers or addiction services).
 - iv. If the pharmacist feels threatened or in danger, contact the police.

Step 3: Clarification of prescription responsibility (prescription delivery)

Once the prescription has been deemed safe and appropriate for the patient and there is no concern for misuse or diversion, the prescription is filled and delivered to the patient. The pharmacist is encouraged to provide patient education.

Limiting Opioids in Clinical Practice continued

7. Pharmacists are encouraged to educate patients regarding opioid medication safety, including risk of side effects, risk of misuse, safe storage and disposal.

- a. Pharmacists are advised to provide patient education regarding safe medication use. Discussion about the potential risks and benefits of opioids can support patients in making informed decisions regarding whether or not to use opioids for pain. Additional resources regarding opioid patient education can be found in **APPENDIX I**.
- b. Patient education is recommended with an initial opioid prescription, and pharmacists are encouraged to offer to review this information with each subsequent fill.⁵⁶
- c. It is recommended that patient education regarding opioid therapy include discussion of at least the following elements:
 - i. Instructions for use, including to take medications as prescribed
 - ii. Potential medication adverse effects, such as constipation, drowsiness, respiratory depression and death
 - iii. Risk of tolerance, dependence and addiction
 - iv. Avoid use of alcohol, other sedating agents and illicit substances concurrent with opioids
 - v. Importance of using one pharmacy for all medications to allow for consideration of drug-drug interactions
 - vi. Proper storage of prescription medications, preferably in a locked container or cabinet
 - vii. Medication should not be shared with others
 - viii. Proper disposal of medications, such as drug take-back events. Additional information on this subject is available within the Harm Reduction section of these guidelines as well as in the resources in **APPENDIX I**.

8. Pharmacists are encouraged to support broadened public access to safe disposal by advocating for local, state and federal efforts aimed at promoting safe disposal of unused medication.

Local, state and/or federal agencies should:

- a. Expand educational outreach to clinicians and the public on safe storage and disposal of excess opioid medication and should increase opportunities for safe drug disposal.

- b. Provide streamlined processes for clinician offices, pharmacies, hospitals and other public locations to become safe disposal sites.
- c. Support the safe disposal of medication via drop-box locations in each county so that safe disposal sites are easily accessible to all Coloradans.
- d. Maintain a database of statewide safe disposal locations to be made available to the public.
- e. Consider providing financial incentives for organizations that participate in safe disposal programs, including pharmacies.
- f. Launch a targeted, statewide public health campaign to educate the public on the importance of safe disposal and statewide locations of safe drug-disposal sites.

9. Pharmacists are encouraged to work collaboratively with other members of the health care team to support opioid-taper strategies.

- a. Pharmacists play an important role in supporting opioid-taper strategies by working collaboratively with the interprofessional team. The determination of taper appropriateness is guided by physician and advanced practice provider assessment. Prescribers can benefit from pharmacist support in achieving slow tapers for patients, particularly those taking long-acting or high-potency formulations. Collaboration with behavioral health specialists may also support coping strategies throughout the opioid taper.
- b. The U.S. Department of Health and Human Services (HHS) *Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics* recommends clinicians consider tapering to a reduced opioid dosage and possibly discontinuing opioid therapy when one or more of the following circumstances exist:⁶⁵
 - i. Pain improves.
 - ii. The patient receives treatment expected to improve pain.
 - iii. The patient requests dosage reduction or discontinuation.
 - iv. Pain and function are not meaningfully improved.
 - v. The patient is receiving higher opioid doses without evidence of benefit.
 - vi. The patient has current evidence of opioid misuse.
 - vii. The patient experiences side effects that diminish quality of life or impair function.

Limiting Opioids in Clinical Practice continued

- viii. The patient experiences an overdose or other serious event (e.g., hospitalization, injury) or has warning signs for an impending event such as confusion, sedation or slurred speech.
- ix. The patient is receiving medications (e.g., benzodiazepines) or has medical conditions (i.e., lung disease, sleep apnea, liver disease, kidney disease, fall risk, advanced age) that increase risk for adverse outcomes.
- x. The patient has been treated with opioids for a prolonged period, and current benefit-harm balance is unclear.
- c. Some patients using both benzodiazepines and opioids may require tapering one or both medications to reduce risk for respiratory depression. It is encouraged that tapering decisions and plans be coordinated with prescribers of both medications. If benzodiazepines are tapered, it is recommended they be tapered gradually due to risks of benzodiazepine withdrawal, which can include anxiety, hallucinations, seizures, delirium tremens and, in rare cases, death.
- d. When initiating an opioid taper, the following points are recommended for consideration:
 - i. It is recommended that when an opioid dosage is reduced, a taper slow enough to minimize opioid withdrawal symptoms and signs be used. Tapering plans should be individualized and based on patient goals and concerns.
 - ii. The longer the duration of previous opioid therapy, the longer the taper may take.
 - iii. Common tapers involve dose reduction of 5-20% every four weeks. Slower tapers (10% per month or slower) are often better tolerated than more rapid tapers, especially following opioid use for more than a year.
 - iv. Longer intervals between dose reductions allow patients to adjust to a new dose before the next reduction.
 - v. Tapers can be completed over several months to years depending on the opioid dose. Faster tapers can be appropriate for some patients.
 - vi. A decrease of 10% of the original dose per week or slower (until 30% of the original dose is reached, followed by a weekly decrease of 10% of the remaining dose) is less likely to trigger withdrawal and can be successful for some patients, particularly after opioid use for weeks to months rather than years.
 - vii. At times, tapers might have to be paused and restarted again when the patient is ready. Pauses may allow the patient time to acquire new skills for management of pain and emotional distress, introduction of new medications or initiation of other treatments while allowing for physical adjustment to a new dosage.
 - viii. Tapers may be considered successful as long as the patient is making progress, however slowly, toward a goal of reaching a safer dose or if the dose is reduced to the minimal dose needed.
 - ix. Once the smallest available dose is reached, the interval between doses can be extended.
 - x. Opioids may be stopped, if appropriate, when taken less often than once a day.
 - xi. More rapid tapers (e.g., over two to three weeks) might be needed for patient safety when the risks of continuing the opioid outweigh the risks of a rapid taper, such as in the case of a severe adverse event such as overdose.
 - xii. Treat symptoms of opioid withdrawal.
 - xiii. Engage with behavioral health services.

Limiting Opioids in Clinical Practice continued

Policy Recommendations

1. Improve PDMPs through interoperability and automated integration into electronic health records (EHRs).

- a. Although the Colorado PDMP is an important tool for reducing inappropriate opioid prescribing, it is cumbersome to use and often incompatible with busy pharmacist workflows both in the community and hospital settings.
- 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 full prescribing information. Access to nationwide data on opioid-prescribing practices would enable pharmacists to better detect aberrant patterns of opioid prescription and encourage their patients to seek treatment.
- c. Legislation is needed to establish a national PDMP and foster the broad exchange of prescribing information.
- d. Providers and pharmacists may be 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.
- e. Automatic queries linked to hospital registration significantly increase the use of PDMPs in clinical decision-making.⁶⁶ Systems that incorporate such technology are overwhelmingly favored by clinicians, 98-100% of whom report improved access.⁶⁷
- f. APhA supports the establishment of a standardized and integrated nationwide PDMP that includes all federal, state and territory databases. APhA supports mandatory PDMP enrollment by all health care providers, mandatory reporting by all those who dispense controlled substances and appropriate system query by registrants during the patient care process related to controlled substances.³²



Alternatives to Opioids for the Treatment of Pain

Alternatives to Opioids for the Treatment of Pain

Using multimodal nonopioid medications and nonpharmacological treatments to address pain is a proven strategy to mitigate pain and reduce community exposure to opioids. The ALTO movement was originally conceptualized in the ED, and most Colorado EDs have successfully implemented ALTO programs.⁶⁸ ALTO is an approach applicable to all medical practices and is a pillar of CO's CURE; it emphasizes understanding and treating all aspects of pain including biologic, psychological and social components. **APPENDIX III, UNDERSTANDING PAIN: A COMPLEX BIOPSYCHOSOCIAL PHENOMENON**, provides a brief overview of how clinicians and pharmacists should conceptualize pain.

In terms of pharmacologic treatment, pain is best addressed by simultaneously intervening at multiple points in the physiological pathways involved in the transmission of pain signals. By selecting pharmacological agents that act on different channels, enzymes and receptors, clinicians can leverage the additive and synergistic mechanisms of analgesia provided by complementary medications to treat pain more comprehensively.

A commonsense approach to reducing the national reliance on opioids is to ensure that every patient requiring pharmacologic treatment of pain is offered nonopioid analgesics and nonpharmacologic pain management modalities as appropriate. Despite evidence in support of multimodal analgesia, clinicians frequently fail to offer patients more than one mode of pain control.⁶⁹ The consistent delivery of multimodal analgesia remains an area of opportunity for reducing opioid use.

Opioid monotherapy often does not achieve adequate analgesia and exposes patients to increased immediate risk of ORADEs and long-term risk of dependence and addiction. For many patients, use of scheduled acetaminophen and an NSAID provides adequate analgesia. For others, the addition of one or more additional nonopioid therapies may reduce or eliminate opioid requirements while simultaneously improving pain control and speeding recovery.⁷⁰⁻⁷² Clinicians who modify their clinical practices to employ more multimodal pharmacologic and nonpharmacologic approaches may deliver better, safer patient care while simultaneously protecting their communities from the harms associated with unused opioid medications.

When selecting multimodal analgesic medications and interventions, clinicians and pharmacists must contend with the lack of high-quality evidence for many of the agents and suggestions outlined in the recommendations below.⁷³ That said, the absence of conclusive findings must be weighed against the incontrovertible evidence of the immediate and long-term harms caused by an overreliance on opioid analgesia, and clinicians are encouraged to consider the relatively safe risk profiles of the many nonopioid options available. It is imperative that pharmacists partner with clinicians, researchers and nurses to define and implement safe and effective analgesic protocols that incorporate available and evolving evidence in a way that is compatible with their unique practice settings.

Practice Recommendations

1. Pharmacists 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.

Alternatives to Opioids for the Treatment of Pain continued

2. Pharmacists are encouraged to apply the ALTO-based pain management protocols found within national and CO's CURE subspecialty guidelines.

- a. Pharmacists are encouraged to be familiar with national evidence-based guidelines that apply to their individual practice settings (**SEE APPENDIX IV**).
- b. CPS members were instrumental in crafting the subspecialty guidelines for the CO's CURE initiative. Each guideline was written by a CPS pharmacist and contains a detailed description of supporting literature, drug information, dosing, cautions and monitoring for each ALTO agent.
- c. While it is beyond the scope of this document to reproduce the ALTO sections of all participating societies' guidelines, pharmacists are encouraged to be familiar with and refer to the guidelines relevant to their area of practice. CO's CURE guidelines are available for the following specialty societies:
 - Society of Hospital Medicine, Rocky Mountain Chapter
 - Colorado Dental Association
 - American College of Emergency Physicians, Colorado Chapter
 - Colorado Pharmacists Society
 - Rocky Mountain Academy of Occupational and Environmental Medicine
 - American College of Surgeons, Colorado Chapter, and Colorado Society of Anesthesiologists
 - American College of Obstetricians and Gynecologists, Colorado Section

3. Pharmacists are encouraged to be familiar with nonpharmacologic therapies and nonopioid pharmacologic therapies for the treatment of pain and encourage care teams and patients to utilize these treatments when clinically appropriate.

- a. Pharmacists can play an important role in patient education related to pain, function goals and safe use of nonopioid pharmacologic and nonpharmacologic therapy for pain.
- b. The HHS Pain Management Best Practices report describes the biopsychosocial model of pain management (**SEE APPENDIX III**).⁷⁴ In this model, the biological, psychological and social factors that contribute to pain are each considered. While pharmacologic pain management primarily targets biological aspects of pain, consideration should also be given to the psychological and social factors that contribute to pain. Non-pharmacologic modalities can be used to address each of these contributors to pain as well.
- c. **TABLE 6** briefly describes many of the evidence-based, non-pharmacologic and procedure-based methods used for management of pain.
- d. Pharmacologic considerations, including the ALTO approach, are essential to pain management. The following are medications routinely used as nonopioid pharmacologic options for pain. For guidance regarding use in particular pain conditions, associated evidence and additional pharmacologic information, please refer to the CO's CURE guidelines for specialty practice.

Alternatives to Opioids for the Treatment of Pain continued

(TABLE 6)

Non-Pharmacologic and Procedure-Based Pain Interventions

<p>Musculoskeletal interventions: ice, heat, stretching, exercise, physical therapy, transcutaneous electrical nerve stimulation (TENS) unit, Epsom salt baths</p>	<p>Pharmacists can recommend musculoskeletal interventions for self-treatment when clinically appropriate, with understanding of contraindications, and should consider situations where referral to the primary care provider or other health care professional is necessary. In such cases, the pharmacist can reach out to the patient's interprofessional team to make the appropriate referrals and interventions.</p>
<p>Interventional procedures: ablation procedures, epidural steroid injections, facet joint nerve block and denervation injection, peripheral nerve injections, sympathetic nerve blocks, neuromodulation, vertebral augmentation, trigger point injections, joint injections</p>	<p>Pharmacists are encouraged to contact the patient's interprofessional team, such as the primary care provider, in order to facilitate referral to an interventional pain specialist for consideration of interventional procedures, as appropriate and indicated.</p>
<p>Mind-body therapy: relaxation techniques (breathing exercises, mindfulness, meditation, stress reduction), cognitive behavioral therapy, behavioral therapy, acceptance and commitment therapy, mindfulness-based stress reduction, psychophysiological approaches, hypnotherapy</p>	<p>Based on training and experience, pharmacists can educate patients about various relaxation techniques. APhA supports integration of a mental health assessment as a vital component of pharmacist-provided patient care services. Pharmacists should reach out to the patient's primary care provider and interprofessional team in order to refer patients to behavioral health as appropriate and indicated.</p>
<p>Integrative health: manipulative therapy (massage, osteopathic manipulation, chiropractic manipulation), bioenergetics therapy (acupuncture), meditative movement therapies (yoga, tai chi), supplements</p>	<p>Pharmacists with training in complementary and integrative approaches to pain management can guide patients in making informed choices about the use of complementary agents/products such as ginseng, peppermint oil, St. John's wort, chamomile and valerian root. The APhA supports pharmacists using professional judgment to make such informed decisions regarding the appropriateness of use or the sale of complementary and alternative medicines. Pharmacists and student pharmacists are encouraged to become knowledgeable about such complementary and alternative medications to facilitate the counseling of patients regarding effectiveness, proper use, indications, safety and possible interactions, along with the use of complementary and alternative medicine (CAM) information databases such as Natural Medicines, CAM on PubMed and the Cochrane Complementary Medicine resource. Expertise in CAM equips pharmacists to further contribute to interprofessional collaboration. Additional CAM educational resources and links to databases: https://guides.hshsl.umaryland.edu/cam</p>

Alternatives to Opioids for the Treatment of Pain continued

(TABLE 7)

ALTO Agents

Class/Mechanism of Action (MOA)	Agents	Type of Pain
Central prostaglandin synthesis inhibitor	Acetaminophen	All
Alpha-2 adrenergic agonists	Clonidine, dexmedetomidine, tizanidine	Neuropathic, opioid withdrawal, perioperative, spasm
Amine reuptake inhibitors/ antidepressants	Amitriptyline, duloxetine, milnacipran, nortriptyline, venlafaxine	Abdominal, extremity, fibromyalgia, migraine/headache, musculoskeletal, neuropathic, perioperative
Antipsychotics	Droperidol, haloperidol, olanzapine	Abdominal, cyclic vomiting, migraine/HA
Beta blockers/calcium channel blockers	Esmolol, propranolol, verapamil	Migraine/HA, perioperative
Calcitonin gene-related peptide (CGRP) receptor agonist	Erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, ubrogepant	Migraine/HA
Contraceptive agents	Depot medroxyprogesterone acetate, etonogestrel implant, levonorgestrel IUD, oral contraceptives	Endometriosis/pelvic, migraine/HA
Dopamine receptor antagonist	Metoclopramide, prochlorperazine	Abdominal, cyclic vomiting, migraine/HA
Gabapentinoids/anticonvulsants	Carbamazepine, gabapentin, oxcarbazepine, pregabalin, topiramate, valproic acid	Dental, fibromyalgia, migraine/HA, musculoskeletal, neuralgia, neuropathic, perioperative
Glucocorticoids	Dexamethasone, methylprednisolone, prednisone	Cancer, dental, migraine/HA, musculoskeletal, perioperative
Gonadotropin-releasing hormone (GnRH) agonist	Buserelin, goserelin, leuprolide, nafarelin, triptorelin	Endometriosis/pelvic
GnRH antagonist	Elagolix	Endometriosis/pelvic
Histamine receptor antagonist	Diphenhydramine, promethazine	Abdominal, cyclic vomiting, migraine/HA
Hormonal agents	Anastrozole, calcitonin, danazol, desmopressin, letrozole, octreotide, oxytocin	Endometriosis/pelvic, migraine/HA, perioperative, renal colic
Inhaled agents	Nitrous oxide	Perioperative, procedural

Alternatives to Opioids for the Treatment of Pain continued

(TABLE 7)

ALTO Agents (continued)

Class/Mechanism of Action (MOA)	Agents	Type of Pain
Local anesthetics/sodium channel blockers	Bupivacaine, lidocaine, ropivacaine	Abdominal, extremity, migraine/HA, musculoskeletal, neuropathic, perioperative, renal colic, dental
Methylxanthines	Aminophylline, caffeine, theophylline	Dental, HA
Muscle relaxants/antispasmodics	Baclofen, cyclobenzaprine, dicyclomine, metaxalone, methocarbamol	Abdominal, fibromyalgia, musculoskeletal, renal colic
Neuromuscular blocker	Botulinum toxin	Abdominal, migraine/HA, musculoskeletal, neuropathic
N-methyl-D-aspartate (NMDA) receptor antagonists	Dextromethorphan, ketamine, magnesium	Migraine/HA, musculoskeletal, neuropathic, perioperative, renal colic
NSAIDs	Aspirin, celecoxib, diclofenac (oral and topical), ibuprofen, indomethacin, ketorolac, ketoprofen, meloxicam, naproxen	Dental, endometriosis/pelvic, migraine/HA, musculoskeletal, perioperative, renal colic
Other topical agents	Camphor, capsaicin, menthol, methyl salicylate	Cyclic vomiting, musculoskeletal, neuropathic
Other oral agents	Ergotamine, hydroxyzine, pentosan polysulfate sodium, phenazopyridine, tamsulosin	Bladder pain syndrome, endometriosis/pelvic, migraine/HA, renal colic, urinary pain
Serotonin receptor agonist	Almotriptan, eletriptan, frovatriptan, lasmiditan, naratriptan, pizotifen, rizatriptan, sumatriptan, zolmitriptan	Migraine/HA

(TABLE 8)

Novel Uses of Agents for Analgesia

Agent	MOA	Type of Pain
Ascorbic acid ⁷⁵	Antioxidant properties	Perioperative
Melatonin ⁷⁵	MT receptor agonist	Cluster headache, perioperative
Memantine	NMDA receptor antagonist	Neuropathic, fibromyalgia, chronic, perioperative
Nicotine	Nicotinic receptor agonist	Perioperative

Alternatives to Opioids for the Treatment of Pain continued

4. As part of the multidisciplinary team involved in patient care, pharmacists are advised to encourage use of ALTOs for pain management across all practice settings, as clinically indicated.

- a. Pharmacists are encouraged to proactively communicate with other members of the health care team regarding opportunities to use ALTOs rather than opioids.
- b. Pharmacists are encouraged to help tailor multimodal analgesic regimens to safely meet the needs of individual patients. It is advised that medication selection and dosages be adjusted based on patient-specific factors, including organ function, comorbidities, home medication regimens and previous medication intolerances. Specific ALTO considerations in special populations include but are not limited to:
 - i. GERIATRIC – Great care should be taken when treating elderly patients. Some of the ALTO therapies suggested may be inappropriate for use in the geriatric population, such as dicyclomine, haloperidol, diphenhydramine and muscle relaxants. *The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults* is a well-established resource to utilize when considering treatment options for patients over 65 years of age.⁷⁶ When possible, consider using topical instead of oral or intravenous routes of administration. Also consider recommending heat, massage and physical therapy for musculoskeletal pain.
 - ii. HEART FAILURE – Not all ALTO agents are recommended for use in patients with heart failure, particularly steroids and NSAIDs. A history of cardiovascular disease may be a contraindication to use of NSAIDs. In those patients where these agents should be avoided, consider use of topical applications.
 - iii. HEPATIC DYSFUNCTION – Not all ALTO agents are safe to use for patients with hepatic dysfunction, particularly intravenous lidocaine and high (> 2 g/day) doses of acetaminophen.
 - iv. PEDIATRICS – Not all ALTO medications and interventions are appropriate for children under 15 years old *OR* over 40 kg. ALTO principles can still be applied for this population, but it is advised that pediatric precautions be considered, and agents dosed appropriately.
 - v. PHARMACOGENOMIC – Pharmacogenetic testing to identify pharmacokinetic and pharmacodynamic variability may be useful in optimizing response to specific medications and decreasing adverse reactions. Pharmacogenomic information is available for certain ALTO medications. Most associations relate to genes that encode drug metabolizing enzymes, with a few related to the human leukocyte antigen (HLA) gene that is associated with the risk of drug hypersensitivity reactions.
 - vi. PREGNANCY – While some ALTO agents may be appropriate to use in pregnant patients, caution is advised. It is recommended that certain agents in the ALTO approach be avoided in pregnancy, such as haloperidol, NSAIDs and valproic acid.
 - vii. RENAL DYSFUNCTION – Not all ALTO agents are safe to use for patients with renal dysfunction, particularly NSAIDs. In patients who cannot receive systemic NSAIDs, consider prescribing topical NSAIDs such as diclofenac gel or patches.
- c. Pharmacists can assist in minimizing the risk of adverse effects by eliminating certain drug-drug combinations, giving a single dose and/or reduced dosages of certain drugs and timing the administration of certain drugs so that they do not reach peak levels simultaneously. Pharmacists can help clinicians understand the administration instructions, benefits and risks of each drug and drug combination.
- d. Pharmacists can recommend pharmacogenomic testing, when appropriate, in order to optimize ALTO therapies and minimize side effects (**SEE APPENDIX V, PHARMACOGENOMIC GUIDANCE FOR USE OF ALTO AGENTS**).
- e. Pharmacists are encouraged to actively participate in the development and implementation of health system pain management policies and protocols, as supported by the American Society of Health-System Pharmacists (ASHP).⁷⁷

Alternatives to Opioids for the Treatment of Pain continued

5. Pharmacists are encouraged to educate patients regarding ALTO therapies.

- a. Pharmacists are encouraged to support patient and caregiver participation in pain management decisions as an integral aspect of patient care.
- b. Pharmacists are encouraged to educate patients regarding safe use of pharmacologic therapy for pain, including opioids and nonopioids.
- c. Pharmacists are encouraged to educate patients regarding non-pharmacologic options for pain and to collaborate with members of the health care team to develop and deliver complete, effective multimodal analgesic plans.
- d. Pharmacists are encouraged to participate in patient education related to clinical goals for pain management. Establishment of these goals is made through shared decision-making with all members of the health care team.

6. Pharmacists are encouraged to collaborate in an interprofessional, team-based approach to managing acute pain in patients on medication for addiction treatment (MAT).

- a. Pharmacists have extensive knowledge of the pharmacologic agents that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of OUD and of the analgesics appropriate for the management of acute pain in patients receiving MAT.

7. Pharmacists are encouraged to engage in continuing education opportunities regarding the use of ALTOs in caring for patients with pain.

- a. As more literature emerges to support the use of ALTOs for pain management, pharmacists are encouraged to stay updated on the latest recommendations and evidence-based treatment pathways.
- b. Resources include:
 - i. The American Chronic Pain Association (ACPA) and APhA collaboration *Taking Care: The Pharmacist's Role in Caring for Patients with Pain*
 - ii. ACPA offers peer support and education in pain management skills to people with pain, family, friends and health care professionals. Its website provides a wealth of information at <https://www.theacpa.org>
 - iii. The American Academy of Pain Medicine offers a number of patient education materials and other resources. This information can be found at <http://www.painmed.org/patientcenter/patient-education/>

8. 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, pharmacists are discouraged from endorsing the use of cannabinoids for pain management).

See APPENDIX VI, CANNABINOIDS AND PAIN, for a brief review of this topic and recommendations for counseling patients.

Alternatives to Opioids for the Treatment of Pain continued

Managing Acute Pain in Patients on Medication for Addiction Treatment

- The use of methadone, buprenorphine or naltrexone for the treatment of OUD may complicate acute pain management.
- It is advised that analgesia be offered to patients receiving MAT who are in acute pain. A patient's usual dose of buprenorphine or methadone is generally inadequate to provide adequate pain control. Splitting home doses of buprenorphine or methadone three times per day leverages the early analgesic effects of these medications, though may not be feasible; however, the analgesic effect is inadequate to address moderate or severe pain.^{78,79}
- It is recommended that the use of pharmacologic and nonpharmacologic ALTOs be maximized in patients receiving MAT.
- The following agents may be of particular value for the treatment of patients receiving MAT:
 - It is recommended that any patient in pain receive scheduled acetaminophen and an NSAID, except when clinically contraindicated.
 - **GABAPENTINOIDS:** Gabapentin (300-600 mg PO three times per day) *OR* pregabalin (75-150 mg PO twice daily) can reduce pain and opioid consumption in hospitalized patients; careful monitoring for over-sedation and respiratory depression is advised.
 - **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 [max 1.2 mg/day, hold if blood pressure < 100/70]; dexmedetomidine 0.2-1 mcg/kg/hr).
 - **NMDA ANTAGONISTS:** Ketamine is the most potent nonopioid analgesic for opioid-tolerant patients. A brief infusion of 0.1-0.3 mg/kg intravenously (IV) over 15 minutes is followed by 0.1-0.3 mg/kg/hr IV infusion. In addition, magnesium is an NMDA receptor antagonist with analgesic and opioid-sparing effects (e.g., 30-50 mg/kg IV bolus followed by 6-20 mg/kg/hr IV infusion).
 - IV lidocaine: A bolus of 1.5 mg/kg is followed by 1-3 mg/kg/hr infusion for analgesia. Contraindications include cardiac dysrhythmias, and cardiac monitoring is recommended.
- It is advised that patients on MAT whose pain is not controlled with nonopioid approaches be offered opioid analgesia; no patient should be denied pain relief. Due to cross-tolerance and increased pain sensitivity, higher-than-typical doses of opioids should be anticipated.
 - As with any patient receiving opioids, it is advised that these patients be monitored closely.
 - For patients receiving buprenorphine for addiction treatment, consider treating acute pain with additional buprenorphine doses.
 - There is no clinical ceiling on buprenorphine for analgesia. Sublingual (SL) buprenorphine can be given as frequently as every two hours. IV buprenorphine is a potent analgesic. Start at 0.3 mg IV and titrate as needed. Respiratory depression does occur at higher doses, but it has a ceiling effect that reduces the baseline by about 50%.⁸⁰
 - Buprenorphine is a partial agonist with a high affinity for the μ -opioid receptor. Thus, for patients receiving buprenorphine with severe acute pain for whom additional opioids are required, it is recommended that clinicians select agents with affinity for the mu-opioid receptor sufficient to displace buprenorphine, such as fentanyl, sufentanil or hydromorphone.
- As a full opioid antagonist, naltrexone blocks the analgesic effects of most opioids. If naltrexone is still present and opioids are necessary, high-dose, high-potency opioids can be used to out-compete naltrexone at the opioid receptor. Patients must be closely monitored, at minimum with pulse oximetry and telemetry, to prevent over-sedation and unintentional overdose.

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

Alternatives to Opioids for the Treatment of Pain continued

Policy Recommendations:

- 1. Require insurance carriers to provide coverage for nonpharmacologic ALTOs and nonopioid medications with established benefits for pain.**
 - a. Health benefit plans should provide coverage for a certain number of physical therapy visits and occupational therapy visits, among other validated nonpharmacologic therapies to address pain.
 - b. CPS supports legislation that increases access to ALTOs through improved insurance coverage. Prohibit insurance carriers from limiting or excluding coverage for a nonopioid medication by mandating that a covered person undergo step therapy or obtain prior authorization if the nonopioid medication is prescribed by the covered person's health care provider. Require the carrier to make the nonopioid medication available at the lowest cost-sharing tier applicable to a covered opioid with the same indication.



Harm Reduction

Harm Reduction

Harm reduction is a public health practice aimed at reducing negative consequences associated with drug use. The approach emphasizes respecting patients and their choices, removing stigma and meeting the patients “where they are” without judgment. In an ideal world, patients would be compelled to stop using drugs by logical clinician and pharmacist counseling. Patients must overcome any external barriers and possess internal resolve to pursue recovery; that process is best aided by building patient trust, which can be accomplished with a harm reduction approach.

Harm reduction practices have been used in recent years when providing services for people who inject drugs (PWID); however, its principles are broadly applicable to most patients with SUD. These practices prevent the spread of infection, including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), hepatitis B and C, skin and soft tissue infections, 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. Even when faced with serious negative consequences of their drug use, many patients are not immediately ready to quit. Given the unprecedented scope and destruction of the opioid epidemic, clinicians and pharmacists can and must do better in counseling, treating and protecting PWIDs from harm until they are ready to enter treatment and recovery.

Pharmacists throughout health care settings can play integral roles in the promotion and implementation of harm reduction strategies and help patients remain safe, even when they are in the midst of battling SUD.

Practice Recommendations

1. It is recommended that patients with OUD be managed without judgment; addiction is a medical condition and not a moral failing. Pharmacists should endeavor to meet patients “where they are,” infusing empathy and understanding into the patient/pharmacist relationship. Behavioral changes should be encouraged but addressed with understanding and patience, incorporating patients’ own motivations and goals.

- a. Pharmacists are encouraged to seek out educational opportunities to better understand addiction and end the stigma associated with OUD and SUD.
- 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 reducing harms and improving health rather than toward moral/societal standards.
 - iii. INDIVIDUALISM – See patients as individuals.
 - 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 medical advice, termination of the relationship often will cause patients 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.
- d. Evidence-based harm reduction strategies, rather than fear- and stigma-driven ultimatums, improve patient and community outcomes.⁸¹ Pharmacists should strive to understand and combat stigma so as to avoid discriminatory actions and/or behaviors and optimize care for patients. Further education and training materials about stigma are available at <https://harmreduction.org/issue-area/issue-drugs-drug-users/understanding-drug-related-stigma/>.

Harm Reduction continued

(TABLE 9)

Counseling Patients with Opioid Use Disorders

DO	DON'T
<ul style="list-style-type: none"> • Use respectful language when discussing patients' drug use. • Assess patients' readiness to change. • Respect patients' decisions regarding treatment. • Encourage patients to be honest with providers about any drug use. • Make information available that is specific to the needs of patients. 	<ul style="list-style-type: none"> • 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.

2. Access to naloxone and overdose education should be widespread. Pharmacists are encouraged to widely recommend naloxone prescription and dispensing in all health care settings, particularly to high-risk patients.

a. Naloxone is an opioid antagonist used to temporarily reverse the effects of opioids in the setting of an overdose. The AACP suggests preparing every student

to provide, administer and educate on appropriate life-saving interventions. The AACP also endorses engaging in educational outreach with other health care providers.²²

b. Pharmacists are encouraged to screen and recognize appropriate candidates to possess naloxone (TABLE 10).

(TABLE 10)

It is advised that naloxone be given or prescribed to high-risk patients, including those who:

- Received care for opioid intoxication or overdose
- Have suspected OUD or nonmedical opioid use
- Are taking > 50 mg morphine equivalents per day
- Are receiving an opioid prescription for pain AND:
 - Are treated with methadone or buprenorphine for OUD
 - Have a history of acute or chronic pulmonary disease
 - Have a history of renal dysfunction, hepatic disease or cardiac comorbidities
 - Have known or suspected excessive alcohol use or dependency
 - Concurrently use benzodiazepines, gabapentinoids or other sedatives
 - Have known or suspected poorly controlled depression
 - Are taking opioids but have unreliable access to emergency medical services
- Have been recently incarcerated/released from prison
- Have resumed opioid use after a period of abstinence

Harm Reduction continued

- c. It is advised that pharmacists be familiar with Colorado's regulations pertaining to naloxone. State laws eliminate liability risk for prescribing naloxone, encourage Good Samaritan reporting of overdose and make naloxone legal and readily available over the counter via standing order in most pharmacies.
 - i. Colorado Third-Party Naloxone Bill (Colorado Senate Bill [SB] 13-014)
 - ii. Colorado Good Samaritan Law (Colorado Revised Statutes [C.R.S.] §18-1-711 and Colorado House Bill [HB] 16-1390)
 - iii. Standing Orders for Naloxone (Colorado SB 15-053)
- d. Pharmacists are encouraged to provide naloxone to individuals through authorized written prescriptions or standing orders (<https://www.colorado.gov/cdphe/naloxoneorders>).
- e. Pharmacists are encouraged to counsel on the appropriate use of naloxone with each prescription authorization and dispensing.
- f. All pharmacies are encouraged to stock and dispense naloxone by authorization of written prescription and/or standing orders. Pharmacies that participate in Colorado's standing naloxone protocols can be found at <http://stoptheclockcolorado.org/> and <https://bringnaloxonehome.org/>.
- g. Pharmacists are encouraged to work with hospitals to establish take-home naloxone programs to provide naloxone to hospitalized patients who are at elevated risk of opioid overdose at discharge. If naloxone cannot be given at time of release, it is recommended that patients receive a prescription and be informed about the over-the-counter availability of the drug via standing order in most Colorado pharmacies.
- h. The following websites have information on overdose education and naloxone distribution and use for pharmacists, patients and other community members:
 - i. <https://cpnp.org/guideline/naloxone/online?view=link-0-1471882249>
 - ii. <https://ernaloxone.org>
 - iii. <https://harmreduction.org>
 - iv. <https://www.samhsa.gov/medication-assisted-treatment/treatment/naloxone>
 - v. <https://prescribetoprevent.org/>

3. Pharmacies are encouraged to provide sale or distribution of sterile syringes and needles without regard to intended use in an effort to decrease the transmission of blood-borne diseases, reduce the incidence of invasive bacterial infections and reduce health care costs.

- a. In PWID, viral infections are often transmitted by the sharing of needles, syringes and other materials used to inject drugs. In 2016, injection drug use directly accounted for 9% of new HIV diagnoses, 13% of new AIDS diagnoses and is believed to have contributed to approximately 20% of new HIV/AIDS diagnoses.⁸² In Colorado, 24% of new HIV diagnoses in women and 17.4% of new HIV diagnoses in men are associated with injection drug use.⁸³
- b. Injection drug use accounts for the majority of new hepatitis C (HCV) infections.⁸⁴ According to the CDC, acute HCV infections increased about 3.5-fold from 2010 through 2016 in the United States. Most cases of acute HCV are not reported as few adults and adolescents with HCV have symptoms, and only a minority of them are diagnosed and reported. After adjusting for this underdiagnosis, the CDC estimates that 41,200 new HCV infections occurred in 2016.^{85,86} 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.⁸⁶ Of the 1,371 case reports of hepatitis B in 2016, over 34.4% of cases indicated use of injection drugs.⁸⁷
- c. Reuse of non-sterile injection equipment increases the risk of soft-tissue and invasive bacterial infections in PWID. 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).⁸⁸ One California based study found that of 169 PWID, 32% (or 54) developed injection-related cellulitis or an abscess.⁸⁹ A 2018 CDC report found that PWID were 16.3 times more likely to develop invasive methicillin-resistant *Staphylococcus aureus* (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 2016.⁹⁰
- d. It is in the best interest of not only the patient, but of

Harm Reduction continued

public health to ensure that PWID have consistent, easy access to sterile injection equipment. This decreases the practice of sharing injection equipment and the need to reuse injection equipment.

- e. Colorado law does not specifically prohibit over-the-counter sales of syringes. Moreover, CPS supports legislation that makes explicit the permission for a pharmacist or pharmacy technician to sell nonprescription syringes or needles to any person and exempts them from drug paraphernalia laws.⁹¹
- f. Pharmacists are encouraged to adopt a harm-reduction approach when caring for PWID by providing or promoting consistent, unrestricted access to sterile syringes, needles and other safe injection equipment. This is consistent with positions taken by the APhA.³²
- g. Pharmacies that do not sell syringes are encouraged to refer patients to community syringe access programs. Colorado Department of Public Health and Environment (CDPHE) maintains a listing of syringe access programs in the state: <https://www.colorado.gov/pacific/cdphe/reducing-infections-injection-drug-us>.

4. Pharmacists are encouraged to educate patients about the safe storage and disposal of syringes and needles.

- a. Pharmacists are encouraged to educate patients that all clean syringes and needles should be stored safely, ideally in a locked location. Syringes should only be used once, never reused. Once syringes are used, it is critical to dispose of them properly to minimize risk of harm or reuse.
- b. Options for the safe disposal of used syringes include sharps collection programs and household disposal. Pharmacists are encouraged to be familiar with these methods for the safe disposal of syringes and to engage with patients and the public regarding safe disposal methods on a regular basis.
- c. Sharps collection programs in Colorado can be found at <https://safeneedledisposal.org/search-results/>.

- d. While disposal using a community sharps collection program is preferred, household disposal may occur if timely disposal cannot occur using a community collection program. Instructions for proper disposal of syringes and sharps at home are as follows:

- i. Use a strong, high-density polyethylene (HDPE) (marked with the #2 symbol) puncture-resistant, leak-proof container with screw-on lid (e.g., laundry detergent bottle with screw-on lid). Place used sharps into the container immediately after use. Do not bend, break or remove needles from syringes. Do not recap or reuse needles. When container is nearly full, replace lid, secure with duct tape, write "USED SHARPS" on the outside and throw it in regular trash (not recycling).

- e. Instructions and handout materials addressing safe sharps disposal is available on the CDPHE website: <https://www.colorado.gov/pacific/cdphe/household-needles-and-sharps> and also <https://safeneedledisposal.org/state-search/>

5. Pharmacies and pharmacists are encouraged to promote public health by providing harm reduction services, including HIV and viral hepatitis testing, HIV prophylaxis, immunizations, promotion of condom use, referral to specialists, referral to social services and education.

Pharmacies and pharmacists are encouraged to:

- a. Offer point-of-care testing for HIV and HCV as recommended by APhA and CPNP.
- b. Support legislation to allow pharmacists to provide pre- and post-exposure prophylaxis medications for HIV under a Colorado statewide standing order.
- c. Provide and promote access to immunizations as indicated, including hepatitis A and B, influenza, pneumococcal polysaccharide (PPSV23) and Tetanus, Diphtheria, Pertussis (Tdap) vaccines.
- d. Provide and promote use of condoms to minimize spread of sexually transmitted infections.
- e. Identify community providers and refer patients to specialists in behavioral health, infectious diseases and addiction treatment.
- f. Identify community resources and refer patients to housing assistance and vocational and recovery support services.

Harm Reduction continued

- g. Provide education and supplies for patient self-management of skin and soft tissue infections. Skin and soft tissue infections remain one of the most common problems in PWID and are experienced by up to one-third of injection drug users. Education may include, but may not be limited to, instruction on proper cleaning, soaking, dressing and providing over-the-counter wound care products or referral for more extensive medical care as needed. Pharmacists are encouraged to caution patients against acquiring antibiotics on the street or manipulating wounds, as this may increase the risk of worsening infections or promote antibiotic resistance.
- h. Visit the CDPHE website for additional resources related to reducing infections (intended for professionals and the general public): <https://www.colorado.gov/pacific/cdphe/reducing-infections-injection-drug-use>
- i. Consider wound-care, continuing medical education for pharmacists. To access the online Accreditation Council for Pharmacy Education course “Advanced Wound Management in the Retail Setting: Role of the Pharmacist,” [click here](#). To download *An Introductory Guide for Assessing and Understanding Common Wounds with People Who Inject Drugs*, [click here](#).

6. Pharmacists are encouraged to support the safe storage and disposal of controlled substances and to consider becoming safe disposal sites.

- a. Prescriptions for controlled substances should be stored safely, ideally in a locked location. Once the medication is no longer needed, it is critical to dispose of leftovers promptly to minimize risk of harm or diversion.
- b. Pharmacists are encouraged to familiarize themselves with all available methods for the safe disposal of controlled substances and to engage with patients and the public on a regular basis regarding safe disposal methods.
- c. Several options exist for the safe disposal of controlled substances, including medication take-back events, medication drop boxes, household disposal and medication mail-back programs.

- i. MEDICATION TAKE-BACK EVENTS – the DEA hosts National Prescription Drug Take Back Days twice each year. Information is available at <https://takebackday.dea.gov/>.
- ii. MEDICATION DROP BOXES – the Colorado Household Medication Take-Back Program accepts and destroys unused and expired over-the-counter and prescription medications, including controlled substances. Further information as well as links to a complete list of collection box locations is available at <https://www.colorado.gov/pacific/cdphe/colorado-medication-take-back-program>.
 - 1. CDPHE encourages pharmacies to participate as collectors in the Colorado Household Medication Take-Back Program. For information on applying to obtain a state-funded, CDPHE-approved collection kiosk for your pharmacy, contact cdphe.commentscpd@state.co.us.
- iii. HOUSEHOLD TRASH DISPOSAL – while medication disposal using a take-back site or program is generally preferred, disposal with household trash may occur if timely disposal cannot occur using an existing program. CDPHE and the FDA provide guidance on disposal of medications at home. In general, do not flush medications.⁹² Flushing can pollute water supplies. Patients may be instructed to follow the steps below for proper trash disposal:
 - 1. Remove medications from their original containers and place in a zip-top bag or a sealable container with a secure lid. Remove labels or cross out any identifying information and recycle or dispose of the bottles separately.
 - 2. Do not crush or attempt to dissolve pills and capsules; mix with an inedible substance such as kitty litter or coffee grounds.
 - 3. Wrap the bag or container in newspaper or a plain brown bag to conceal its contents.
 - 4. Place in trash on the day of collection.
- d. FDA resources for reference:
 - i. <https://www.fda.gov/drugs/disposal-unused-medicines-what-you-should-know/drug-disposal-dispose-non-flush-list-medicine-trash>
 - ii. <https://www.fda.gov/media/109643/download>

Harm Reduction continued

Policy Recommendations

1. **Funding for harm reduction agencies and community resources for PWID should be greatly expanded in areas of Colorado that are currently lacking; pharmacies can be a key element to extending such critical harm reduction services.**
 - a. The passage of C.R.S. §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. Funding should be extended to pharmacy-based services who voluntarily participate in such programs as well in order to sustain such valuable programs.
2. **Legislation should be changed to make explicit the permission for a pharmacist or pharmacy technician to sell nonprescription syringes or needles to any person, and to exempt pharmacists and pharmacy technicians from drug paraphernalia laws.**
 - a. The potential legal constraint to pharmacy sale of syringes in Colorado is a drug paraphernalia statute based on the DEA Model Drug Paraphernalia Act of 1979.
 - b. Pharmacists and technicians currently face concerns related to C.R.S. §18-18-429, which states that a person who sells syringes or needles that are known for use as drug paraphernalia commits a level 2 drug misdemeanor.
 - c. Future legislation (such as proposed Colorado HB 20-1065 Harm Reduction Substance Use Disorders) should clarify permission of a pharmacist or technician to sell nonprescription syringes or needles to any person and should eliminate the concerns related to drug paraphernalia rules.



Treatment of Opioid Use Disorder

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.⁹³ The consequences of this treatment gap are substantial, including dramatically increased risks of overdose injury and death, transmission of HIV, viral hepatitis, invasive bacterial infections and a range of risky and criminal behaviors. Medicine now recognizes that OUD is a chronic, relapsing disease. Like patients with other chronic illnesses, patients with OUD need ongoing comprehensive, evidence-based care. Abstinence-oriented treatments are generally ineffective for the treatment of OUD, with relapse rates of greater than 80%.⁹⁴ The gold standard for treatment of OUD employs one of the three FDA-approved medications for OUD: methadone, buprenorphine or naltrexone. People receiving MAT can lead fulfilling, productive lives while maintained on medication. It is important to recognize that opioid dependence and opioid addiction are different entities; patients may be physically dependent on buprenorphine or methadone, but when maintained on these medications the risks and behaviors seen in addiction are avoided.

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.⁹⁵ As many pharmacists are aware, a quarter or more of patients with OUD will leave the hospital against medical advice due to craving, withdrawal, fear of stigma or mistreatment or social pressures.⁹⁶ Patients whose withdrawal is managed with buprenorphine or methadone are less likely to leave against medical advice and have shorter, less complicated admissions.^{97,98} 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.⁹⁹ Pharmacists are ideally positioned to help people with untreated OUD access care. The stigma surrounding OUD leads some patients to conceal their disease, while past negative experiences with the health care system make other patients wary of medical providers. Pharmacists can screen patients consistently and offer help to patients with OUD in a non-stigmatizing, compassionate manner.

Pharmacists, as front-line health care professionals, play a key role in educating providers and patients about MAT, identifying risk factors for OUD and participating in a multidisciplinary team to assist in the management of patients with OUD.

Practice Recommendations

1. Pharmacists are encouraged to have a basic understanding of OUD and the importance of medical treatment.

- a. OUD, and SUD more generally, are poorly understood by many medical professionals. Despite the fact that overdose is the leading cause of death in Americans under the age of 50, as of 2018 fewer than 10% of medical schools had a formal addiction curriculum.¹⁰⁰ While the AACP recommends that schools of pharmacy direct teaching and research activities toward reducing the public health threat from OUD, it is unknown to what extent programs are choosing to do so. Pilot programs providing in-depth education on OUD have shown that increasing pharmacy student knowledge about OUD and its treatment may decrease associated stigma.^{22,101}
- b. OUD as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) replaces “opioid addiction” and “opioid dependence” as a diagnostic

entity.¹⁰² The DSM-5 defines OUD using the 11 criteria listed in **TABLE 11**. 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 criteria indicates severe OUD.

- c. Of note, physiologic dependence represents only two of the 11 criteria used to diagnose OUD. Patients receiving COT for chronic pain often exhibit pharmacological dependence but would not necessarily be considered to have OUD.
- d. 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 four C’s of addiction: loss of Control, use despite negative Consequences, Compulsive use and Cravings.

Treatment of Opioid Use Disorder continued

(TABLE 11)

Summarized DSM-5 Diagnostic Categories and Criteria for OUD

CATEGORY	CRITERIA
Impaired Control	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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-5¹⁰²

- e. Abstinence-based therapies are largely ineffective for the treatment of OUD. Pharmacists are encouraged to not routinely recommend abstinence-based treatments for OUD.¹⁰³
- f. 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.
- g. Most patients with OUD are not adequately treated. As of 2019, the Colorado Department of Human Services Office of Behavioral Health estimates a treatment gap of approximately 70%, with only 30% of patients with OUD receiving treatment.
- h. It is advised that patients and pharmacists 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.¹⁰⁴

- i. See Appendix VII, Additional Resources for OUD Assessment and Diagnosis.

2. It is recommended that a comprehensive, evidence-based approach be used to manage OUD, emphasizing the use of MAT.

- a. 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.¹⁰⁵
- b. 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 treatment” to distinguish them from naltrexone, which is a full opioid antagonist. **TABLE 12** describes different characteristics of MAT drugs.

Treatment of Opioid Use Disorder continued

(TABLE 12)

Characteristics of Medications for Opioid-Addiction Treatment

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; Suboxone diminishes this risk by including naloxone, 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: NEJM³³⁸

Treatment of Opioid Use Disorder continued

- c.

It is advised that the decision to initiate MAT and the choice of MAT medication be a shared decision with the patient and the treatment team. Unlike methadone, which requires a referral to a federally licensed program, buprenorphine can be dispensed in primary care settings. An X-waiver is required to
- prescribe buprenorphine in outpatient settings. There are no restrictions or waivers required for prescribing naltrexone. Additional considerations can be found in **TABLE 13.**

<div>(TABLE 13)</div> <div>Special Pharmaceutical Considerations for MAT Drugs</div>	
Buprenorphine	<ul style="list-style-type: none">• Available in an oral tablet, a sublingual tablet, a buccal tablet, an implanted device and a long-acting injection.• Diversion and misuse are possible. Buprenorphine is available in formulations with naloxone, which is added as a deterrent to IV use.• Patients can form physical dependence to buprenorphine.• Risk of respiratory depression when used with CNS depressants.• Dose adjustment recommended in hepatic impairment.
Methadone	<ul style="list-style-type: none">• Used in treatment of chronic pain or OUD.• In the treatment of OUD is only available in the setting of federally and state approved opioid treatment program (OTP).• Numerous and significant adverse drug effects including respiratory depression, paralytic ileus, cardiac conduction effects (causes significant QT prolongation).• Drug interactions with medications metabolized by CYP34A, CYP2B6, CYP2C19 and to a lesser extent by CYP2C9 and CYP2D6.• Methadone used for OUD is not reported in the Colorado PDMP.
Naltrexone	<ul style="list-style-type: none">• Considered to be less effective than methadone and buprenorphine due to limited adherence.¹⁰⁷• Patient should be opioid-free for seven to 10 days before administering naltrexone to avoid precipitating withdrawal.• Can be administered by pharmacists with shared service agreement.<ul style="list-style-type: none">- Dosage of 380 mg IM gluteal injection every four weeks.• Upon cessation patients are more vulnerable to overdose.• Risks include precipitated opioid withdrawal, hepatotoxicity, eosinophilic pneumonia.• Causes significant problems for acute pain and surgery as it significantly decreases the efficacy of opioids. Should be discontinued prior to elective procedures and surgeries.

- d.

Additional guidance and important related publications can be found in **APPENDIX VIII, ADDITIONAL RESOURCES FOR OUD TREATMENT.**

Treatment of Opioid Use Disorder continued

3. Pharmacists are encouraged to support MAT efforts through the administration of long-acting injectables.

- a. In 2019, the Colorado Department of Health Care Policy and Financing implemented HB 18-1007, which stipulates that if a pharmacy has entered into a collaborative practice agreement with one or more physicians for the purposes of administering IM long-acting naltrexone, that the pharmacy where the injection is administered shall receive reimbursement when an enrolled pharmacist administers it. This improves access to administered long-acting injectables for MAT, can improve adherence and enable a more rapid initiation of therapy.
- b. CPS supports legislation (such as Colorado SBs 18-168 and 20-007) that provides qualified pharmacists with an enhanced reimbursement rate for administration of long-acting naltrexone and any future FDA-approved injectable drug that is allowed to be administered by pharmacists.
 - i. Pharmacists who are in a collaborative practice agreement with a prescriber should receive an increased dispensing fee from Health First Colorado and other public and private insurers for administering injectable MAT. This dispensing fee should align with the administration fee that would be provided to a clinician if the MAT was administered in the clinician's office.
 - ii. Providing pharmacists with an enhanced dispensing fee or other compensation for administration of Vivitrol (naltrexone) and any future FDA-approved injectable drug that is allowed to be administered by pharmacists offers an incentive for these providers to administer the drug.
- c. Instructions on how to enroll and properly bill as a pharmacist can be found here: <https://www.colorado.gov/pacific/hcpf/otc-immunizations>

4. Pharmacists are encouraged to engage with the multidisciplinary team to assist in the management of patients with OUD.

- a. Optimal care for patients with OUD involves a team approach. Patients do best when their physiologic dependence and cravings are managed with MAT and they receive social support, recovery support and behavioral health care as appropriate.
- b. Pharmacists are an essential component of the care team, serving as medication experts able to assist in initial medication selection for MAT, identify adverse drug events during treatment, monitor medication adherence, offer continued vigilance for risk factors and aberrant behaviors, and can facilitate access to MAT medications.
- c. Pharmacists can administer injectable MAT medications through a collaborative practice agreement.

5. Pharmacists are encouraged to engage in continuing education regarding the management of patients with OUD.

- a. Pharmacists are encouraged to maintain their knowledge of best practices, recommendations and evidence for OUD treatment.
- b. Additional Resources:
 - i. National Institute on Drug Abuse: <https://www.drugabuse.gov/drugs-abuse/opioids>
 - ii. Substance Abuse and Mental Health Services Administration (SAMHSA): <https://www.samhsa.gov/find-help/treatment#opioid>
 - iii. American Psychiatric Association: <https://www.psychiatry.org/patients-families/addiction/opioid-use-disorder/opioid-use-disorder>
 - iv. Opioid Use Disorders: Interventions for Community Pharmacists, a CPNP guideline document: <https://cpnp.org/ed/presentation/2016/opioid-use-disorders-interventions-community-pharmacists?view=link-0-1471880668>

Treatment of Opioid Use Disorder continued

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.
- b. Barriers for clinicians to prescribe FDA-approved medications exist and should be removed.
- c. Treatment plans are best left to clinicians, and drugs that are approved by the FDA for MAT should be equally available and accessible.
- d. Extended-release opioid antagonists for MAT should be included in the pharmacy benefit for the Colorado Medicaid program, Health First Colorado. Under this recommendation, all three of the MAT medications should be codified into the pharmacy benefit of the Colorado Health First program and ensure that coverage of these medications persists through administrations and any future budget decisions.

2. Repeal the X-waiver requirement for prescribing buprenorphine. Alternatively, legislation could be modified to allow pharmacists to prescribe and manage MAT as part of an integrated care team.

- 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.
- 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, American Academy of Emergency Medicine, American Academy of Clinical Toxicology, American Society of Addiction Medicine and ASHP.
- d. Alternatively, legislation could be changed to modify the X-waiver system to allow pharmacists to prescribe and manage MAT as part of an integrated care team. This is in alignment with ASHP efforts to address the opioid epidemic by expanding pharmacists' ability to treat opioid addiction.

- e. CPS supports the Mainstreaming Addiction Treatment Act of 2019 (U.S. House Resolution 2482) and any similar acts designed to eliminate the requirement for medical providers to obtain a waiver from the DEA to treat OUD with buprenorphine or any other Schedule III, IV or V drug. Such action would significantly aid in closing the treatment gap and reducing overdose deaths.

3. Ease regulations around HHS 42 CFR Part 2 to ease the sharing of critical health data.

- a. 42 CFR Part 2 requires any patient with SUD to provide explicit permission for an OTP or treating provider to share information about their medical care, even with other clinicians and pharmacists caring for the patient.
- b. 42 CFR provided an essential safeguard for privacy from 1975 until the Health Insurance Portability and Accountability Act (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, hospital-based physicians and pharmacists are left unaware of a patient's maintenance on methadone.
- d. This proves dangerous when pharmacists dispense prescribed QT-prolonging drugs, benzodiazepines or other medications that interact with methadone, resulting in potentially fatal drug interactions.
- e. The separation of SUD from the rest of medicine further stigmatizes a disease process that should be normalized.
- f. CPS 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 and other entities outside the patient-pharmacist relationship.
- g. CPS joins the American Medical Association (AMA), American Hospital Association, American Society of Addiction Medicine, ASHP and others in the call to better align SUD treatment with the rest of medicine.

Treatment of Opioid Use Disorder continued

4. Telemedicine for addiction treatment should be made widely available, and telemedicine providers should be able to prescribe buprenorphine without a face-to-face encounter. Legislation should be changed to allow pharmacists to prescribe and manage MAT as part of an integrated care team, as this could significantly contribute to the availability of such services in rural areas of Colorado.

- a. The 2018 Special Registration for Telemedicine Clarification Act directs the DEA to amend its rules regarding the face-to-face encounter required by the 2008 Ryan Haight Act when prescribing controlled substances.
- b. The Ryan Haight Act in effect eliminates the ability of clinicians to treat patients with OUD in rural areas, posing an unnecessary obstacle 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. It is encouraged that the act's restrictions be loosened to allow for telehealth prescription of buprenorphine in order to allow clinicians to better treat patients in rural and other hard to access areas.
- e. CPS supports legislation that would eliminate the barrier preventing pharmacists from prescribing and dispensing buprenorphine for MAT or OUD. In addition to expansion of telemedicine services, this could greatly contribute to shrinking the current treatment gap for OUD in rural areas of Colorado.

The Future and Ending the Opioid Epidemic in Colorado

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

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

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

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

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Appendices

- I. Additional Resources for Limiting Opioids
- II. Pharmacogenomic Guidance for Opioid Therapy
- III. Understanding Pain: A Complex Biopsychosocial Phenomenon
- IV. Links to National Society Pain Treatment Guidelines
- V. Pharmacogenomic Guidance for Use of ALTO Agents
- VI. Cannabinoids and Pain
- VII. Additional Resources for OUD Assessment and Diagnosis
- VIII. Additional Resources for OUD Treatment

Appendix I

Additional Resources for Limiting Opioids

APhA Opioid Use and Misuse Resource Center

This resource center links to a variety of resources that pharmacists may find useful, including tools, clinical and patient resources, training resources, and state and federal updates.

<https://www.pharmacist.com/opioid-use-and-misuse-resource-center>

Colorado Consortium for Prescription Drug Abuse Prevention

The Colorado Consortium for Prescription Drug Abuse Prevention is a sponsor of these guidelines and is leading efforts across the state to reduce opioid abuse. The organization's website has many helpful resources and tools that pharmacists may find useful, including but not limited to provider education resources, information about medication storage and disposal, naloxone-related resources and the Community Reference. The Community Reference is a resource guide to support local communities in combating the opioid crisis.

MAIN WEBSITE: <http://www.corxconsortium.org/>

COMMUNITY REFERENCE: <http://www.corxconsortium.org/communityreference/>

SBIRT and Motivational Interviewing Information and Free Training

SBIRT is a comprehensive, integrated approach to early intervention for persons with SUD. SBIRT uses motivational interviewing strategies that pharmacists may already be familiar with. To learn more about SBIRT, visit the SAMHSA website: <https://www.samhsa.gov/sbirt/about>.

The SBIRT in Colorado program also offers free in-person or online training for those interested in learning more: <http://www.sbirtcolorado.org/>. For those interested in additional general motivational interviewing training, consider the comprehensive motivational interviewing training available from National Community Pharmacists Association or using a text for self-directed learning. (Example text: Rollnick S, Miller WR, and Butler CC. Motivational Interviewing in Health Care: Helping Patients Change Behavior. New York, New York: The Guilford Press; 2008. 210 pages, \$25, ISBN-13:978-1-59.85-612-0.)

Take Meds Seriously

This resource is a patient education tool regarding safe use, storage and disposal of prescription medications. While this source does have a focus on safe use of opioids, these principles could be used to educate regarding safe use of all medications. Key educational messages include considering an opioid pain reliever a serious medication and using only as directed, storing medications in a secure location to limit diversion and disposing of opioids in a safe disposal location whenever possible.

WEBSITE: <https://takemedsseriously.org/>

Appendix II

Pharmacogenomic Guidance for Opioid Therapy

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) have published peer-reviewed, evidence-based guidelines for CYP2D6 and opioids.^{38,39} Additionally, some FDA drug labels carry PGx biomarker information that provides information on drug dosing (<https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling>). Genetic polymorphism in CYP2D6 results in four metabolizer phenotypes: ultrarapid (UM), normal (NM), intermediate (IM) and poor metabolizers (PM). The hepatic CYP2D6 enzyme activates prodrugs, like codeine to morphine and tramadol to O-desmethyltramadol, with these metabolites having higher affinity for the μ -opioid receptor than the parent compounds. CYP2D6 also converts oxycodone to oxymorphone and hydrocodone to hydromorphone, with both parent drug and metabolites having μ -receptor agonist activity but the metabolites have greater μ -receptor affinity.^{38,40} **TABLE 14** shows the opioid therapy recommendations based on CYP2D6 metabolizer phenotypes.

Studies in patients who are CYP2D6-UM have reported increased incidence of adverse effects such as respiratory depression and nausea when patients were prescribed

codeine and tramadol. As such, guidelines recommend avoiding codeine and tramadol in CYP2D6-UM and to use alternative opioids not affected by CYP2D6, such as morphine, oxymorphone, fentanyl, buprenorphine, methadone and hydromorphone, or nonopioid analgesics. For patients who are CYP2D6-IM, there is decreased formation of the active metabolite of codeine and tramadol leading to poor analgesic response, with guidelines recommending monitoring for analgesic response and switching to alternative opioids or nonopioid analgesics if there is no analgesic response. This reduction in analgesic response is even more significant among CYP2D6-PM where codeine and tramadol should be avoided due to their lack of efficacy. Patients should be switched to alternative opioids not affected by CYP2D6 or nonopioid analgesics instead based on the indication. Due to the limited number of studies conducted with hydrocodone and oxycodone in CYP2D-UM and PM, guidelines recommend avoiding them in CYP2D6-UM and PM, given their metabolism is affected by CYP2D6, and to instead use alternative opioids not affected by CYP2D6 or nonopioid analgesics.

Appendix II continued

(TABLE 14)

Opioid Therapy Recommendations Based on CYP2D6 Metabolizer Phenotypes

CYP2D6 Phenotype	CYP2D6 Phenotype
Ultrarapid Metabolizer (UM)	<ul style="list-style-type: none"> • Avoid codeine and tramadol due to increased formation of their respective active metabolites leading to increased risk of toxicity. • For hydrocodone and oxycodone that form active metabolites (in addition to the active parent drug), data for ultrarapid metabolizers are limited so guidelines recommend using alternative analgesics instead. • Alternative analgesics not affected by CYP2D6 metabolism include opioids (such as morphine, oxymorphone, fentanyl, buprenorphine, methadone and hydromorphone) or nonopioid analgesics to be selected based on the indication.
Normal Metabolizer (NM)	<ul style="list-style-type: none"> • Use standard dose of opioid.
Intermediate Metabolizer (IM)	<ul style="list-style-type: none"> • For codeine and tramadol, there is decreased formation of their respective active metabolite leading to poor analgesia. Monitor for analgesic response and consider alternative analgesics if no response. • Alternative analgesics not affected by CYP2D6 metabolism include opioids (such as morphine, oxymorphone, fentanyl, buprenorphine, methadone and hydromorphone) or nonopioid analgesics to be selected based on indication.
Poor Metabolizer (PM)	<ul style="list-style-type: none"> • Avoid codeine and tramadol due to the reduction in formation of their respective active metabolites leading to poor analgesia. • For hydrocodone and oxycodone that form active metabolites (in addition to the active parent drug), data for poor metabolizers are limited so guidelines recommend using alternative analgesics instead. • Alternative analgesics not affected by CYP2D6 metabolism include opioids (such as morphine, oxymorphone, fentanyl, buprenorphine, methadone and hydromorphone) or nonopioid analgesics to be selected based on indication.

Appendix III

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 pharmacists 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.

Pharmacists are encouraged to recommend 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.¹⁰⁸⁻¹¹⁰

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.¹¹¹⁻¹¹³ 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.¹¹⁴ Studies have also identified measurable electroencephalogram signatures capable of predicting differences in pain tolerance between individuals.¹¹⁵

The Psychology of Pain

Neuroimaging studies demonstrate the significant extent to which cognitive and affective factors impact the experience of pain. The anticipation of pain 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.

Appendix III continued

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.¹¹⁶⁻¹¹⁸

Finally, it is important to acknowledge the critical role that clinician empathy can play in promoting pain relief.¹¹⁹ Because the psychology of patient-clinician interactions influences the way patients experience pain and analgesia, clinician desensitization to pain complaints can undermine the quality of care and decrease the provider's professional satisfaction.¹²⁰ Clinicians 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 pharmacists 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.¹²¹ 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 be easily 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.¹²²

To an extent not seen with other conditions, the biology of pain is the sociopsychology of pain. It is vital for pharmacists 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. Clinicians serve their patients best when they involve pain specialists, mental health providers, physical therapy, pharmacists and social workers in the management of patients with complex pain presentations.

Appendix IV

Links to National Society Pain Treatment Guidelines

American Academy of Neurology

- *Practice Guideline Update Summary: Botulinum Neurotoxin for the Treatment of Blepharospasm, Cervical Dystonia, Adult Spasticity, and Headache 2016*
<https://www.aan.com/Guidelines/home/GuidelineDetail/735>
- *Pharmacologic Treatment for Episodic Migraine Prevention in Adults 2012*
<https://www.aan.com/Guidelines/home/GuidelineDetail/536>
- *Guidelines for the Prevention of Episodic Migraine 2012*
<https://headachejournal.onlinelibrary.wiley.com/doi/full/10.1111/j.1526-4610.2012.02185.x>
- *Acute and Preventive Pharmacologic Treatment of Cluster Headache 2010*
<https://www.aan.com/Guidelines/home/GuidelineDetail/448>
- *Efficacy of Transcutaneous Electric Nerve Stimulation in the Treatment of Pain in Neurologic Disorders 2010*
<https://www.aan.com/Guidelines/home/GuidelineDetail/382>
- *The Diagnostic Evaluation and Treatment of Trigeminal Neuralgia 2008*
<https://www.aan.com/Guidelines/home/GuidelineDetail/301>

American Academy of Pain Medicine

<https://painmed.org/clinician-resources/clinical-guidelines>

American College of Emergency Physicians

<https://www.acep.org/globalassets/new-pdfs/clinical-policies/opioids-2012.pdf>

American College of Occupational and Environmental Medicine

<https://acoem.org/Guidance-and-Position-Statements/Guidelines>

American College of Physicians

- *Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain Guidelines 2017*
<https://www.acpjournals.org/doi/10.7326/M16-2367>

American College of Rheumatology/Arthritis Foundation

- *Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee 2019*
<https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Osteoarthritis>

American Diabetes Association

- *Standards of Medical Care in Diabetes—Microvascular Complications and Foot Care 2020*
https://care.diabetesjournals.org/content/43/Supplement_1/S135

American Headache Society

- *Treatment of Cluster Headache Evidence-Based Guidelines 2016*
<https://headachejournal.onlinelibrary.wiley.com/doi/full/10.1111/head.12866>
- *Management of Adults with Acute Migraine in the Emergency Department*
<https://headachejournal.onlinelibrary.wiley.com/doi/full/10.1111/head.12835>
- *Guidelines for the Prevention of Episodic Migraine 2012*
<https://headachejournal.onlinelibrary.wiley.com/doi/full/10.1111/j.1526-4610.2012.02185.x>

Appendix IV continued

Institute for Clinical Systems Improvement

- *Pain: Assessment, Non-Opioid Treatment Approaches, and Opioid Management Guideline 2017*
<https://www.icsi.org/guideline/pain/>

National Comprehensive Cancer Network

- *Adult Cancer Pain Guidelines*
https://www.nccn.org/professionals/physician_gls/default.aspx

Orthopaedic Trauma Association

- *Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury*
https://journals.lww.com/jorthotrauma/FullText/2019/05000/Clinical_Practice_Guidelines_for_Pain_Management.11.aspx

Society of Critical Care Medicine

- *2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS)*
https://journals.lww.com/ccmjournal/Fulltext/2018/09000/Clinical_Practice_Guidelines_for_the_Prevention.29.aspx

United States Department of Health and Human Services

- *Pain Management Best Practices 2019*
<https://www.hhs.gov/ash/advisory-committees/pain/index.html>

U.S. Department of Veterans Affairs/Department of Defense

- *Diagnosis and Treatment of Low Back Pain Clinical Practice Guidelines 2017*
<https://www.healthquality.va.gov/guidelines/pain/lbp/index.asp>

Appendix V

Pharmacogenomic Guidance for Use of ALTO Agents

(TABLE 15)

ALTO Agents with Pharmacogenomic Information Available in CPIC, DPWG Guidelines and FDA Drug Labels

Class/MOA	Agents	Genes Involved	Dosing Recommendations
Amine reuptake inhibitors/antidepressants	Amitriptyline ¹	CYP2C19 and CYP2D6	<p>CPIC recommendations apply to higher antidepressant doses rather than lower doses used to treat neuropathic pain. No adjustments needed if used at low doses for neuropathic pain dose but monitor for drug response and side effects.¹</p> <ul style="list-style-type: none"> a. CYP2C19 UM, RM and PM: Avoid amitriptyline. b. CYP2D6 UM and PM: Avoid amitriptyline. c. For CYP2C19 NM/CYP2D6 NM: Initiate standard amitriptyline dose d. For CYP2C19 IM/ CYP2D6 NM: Initiate standard amitriptyline dose e. For CYP2C19 NM/CYP2D6 IM: Consider a 25% reduction in starting dose f. For CYP2C19 IM/ CYP2D6 IM: Consider a 25% reduction in starting dose
	Nortriptyline ¹	CYP2D6	<p>CPIC recommendations apply to higher antidepressant doses rather than lower doses used to treat neuropathic pain. No adjustments needed if used at low doses for neuropathic pain dose but monitor for drug response and side effects.¹</p> <ul style="list-style-type: none"> a. UM: Avoid nortriptyline due to the potential lack of efficacy. b. IM: Consider a 25% reduction in starting dose c. PM: Avoid nortriptyline due to the potential risk for side effects. If use is warranted, consider a 50% reduction in starting dose.
	Venlafaxine ²	CYP2D6	<ul style="list-style-type: none"> a. IM/PM: Use an alternative drug or reduce dose due to the increased risk for side effects. b. UM: Use an alternative drug or increase dose to 150% of standard dose due to increase metabolism of parent to its active metabolite.
Antipsychotic	Haloperidol ²	CYP2D6	<p>PM: Use an alternative drug or reduce starting dose by 50% and adjust dose based on response.</p>

Appendix V continued

(TABLE 15)

ALTO Agents with Pharmacogenomic Information Available in CPIC, DPWG Guidelines and FDA Drug Labels (continued)

Class/MOA	Agents	Genes Involved	Dosing Recommendations
Gabapentinoid/ anticonvulsants	Carbamazepine ³	HLA-A*31:01 and HLA-B *15:02	<ul style="list-style-type: none"> a. HLA-B*15:02 positive and any HLA-A*13:01 genotype (positive or negative): <ul style="list-style-type: none"> i. Avoid carbamazepine if patient is carbamazepine-naïve due to the risk of cutaneous adverse reactions such as Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). ii. Cautiously consider carbamazepine use if patient has previously used drug for >3 months without evidence of cutaneous adverse reactions. b. HLA-B*15:02 negative and HLA-A*31:01 positive: <ul style="list-style-type: none"> i. Avoid carbamazepine if patient is carbamazepine-naïve due to the risk of cutaneous adverse reactions such as SJS/TEN, drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE). ii. If alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue carbamazepine at first evidence of a cutaneous adverse reaction. iii. Cautiously consider use if patient has previously used carbamazepine for >3 months without evidence of cutaneous adverse reactions.
	Oxcarbazepine ³	HLA-B*15:02	<p>HLA-B*15:02 positive:</p> <ul style="list-style-type: none"> i. Avoid oxcarbazepine if patient is oxcarbazepine-naïve due to the risk of cutaneous adverse reactions such as SJS/TEN. ii. Cautiously consider use if patient has previously used oxcarbazepine for >3 months without evidence of cutaneous adverse reactions.
Hormonal agents	Hormonal contraceptives ²	Factor V	Avoid estrogen-containing oral contraceptives in patients with Factor V Leiden allele and have a family history of thrombotic events or previous thrombosis.

Appendix V continued

(TABLE 15)

ALTO Agents with Pharmacogenomic Information Available in CPIC, DPWG Guidelines and FDA Drug Labels (continued)

Class/MOA	Agents	Genes Involved	Dosing Recommendations
NSAIDs	Celecoxib ⁴ Flurbiprofen ⁴ Ibuprofen ⁴ Meloxicam ⁴ Piroxicam ⁴	CYP2C9	<p><i>Recommendations are based on half-life of these NSAIDs</i></p> <p><u>CYP2C9-IM (activity score = 1)</u></p> <ul style="list-style-type: none"> For short-acting NSAIDs (celecoxib, flurbiprofen and ibuprofen): use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. For intermediate-acting NSAID (meloxicam): To initiate at 50% of the lowest starting dose and titrate after at least one week. To titrate up to 50% of maximum recommended dose with caution or use alternative NSAIDs. For long-acting NSAID (piroxicam): Avoid piroxicam due to increased risk for adverse effects associated with its reduced metabolism and prolonged half-life. Use alternative NSAIDs. <p><u>CYP2C9-PM</u></p> <ul style="list-style-type: none"> Initiate short-acting NSAID (celecoxib, flurbiprofen and ibuprofen) at 25-50% of the lowest starting dose and titrate gradually after reaching steady state levels (at least eight days for celecoxib and five days for ibuprofen). Titrate up to 25-50% of the maximum recommended dose with caution. Avoid using meloxicam and piroxicam due to significant reduction in their metabolism and prolonged half-lives, which increase the risk of adverse effects. Use alternative NSAIDs. <p><u>Alternative NSAIDs</u> not significantly affected by CYP2C9 include aspirin, ketorolac, naproxen and sulindac.</p>
Local anesthetic/ sodium channel blocker	Lidocaine ⁵ Ropivacaine ⁶	G6PD	Caution use in patients with G6PD deficiency or congenital methemoglobinemia as they are more susceptible to drug-induced methemoglobinemia.
NMDA receptor antagonist	Dextro-methorphan ⁷	CYP2D6	PMs may be at risk of experiencing dextromethorphan toxicity, but no dosing recommendations are available.
Dopamine receptor antagonist	Meto-clopramide ⁸	CYP2D6	PM: Reduce dose due to increased risk for side effects with maximum recommended daily dosage of 30 mg (for gastroesophageal reflux) or 20 mg (for diabetic gastroparesis).
Other oral agent	Tamsulosin ⁹	CYP2D6	PM: Use with caution at doses >0.4 mg due to increased tamsulosin exposure in PM

Appendix VI

Cannabinoids and Pain

Cannabinoids and Pain: Counseling Patients

- As of this writing, no definitive, high-quality studies support the safety and efficacy of dispensary or pharmaceutical cannabinoids for analgesia in chronic, noncancer pain. Until better evidence is available, pharmacists are discouraged from endorsing the use of cannabinoids for pain management.
- It is recommended that any patient with chronic pain should be encouraged to seek care from a pain medicine specialist.
- It is suggested that patients be counseled that the use of any drug that lacks rigorous FDA drug development and safety profiles carries inherent risks.
 - The testing and regulation of dispensary cannabis is poor to nonexistent.
 - Products purchased at dispensaries may be mislabeled, of undetermined content and/or contaminated with harmful substances.
 - It is important to remind patients that cannabis dispensary workers are not trained to give medical advice.
- Adverse effects associated with cannabinoid use include:
 - The development of cannabis use disorder (CUD)
 - Historically, one in 10 cannabis users—and one in six users under the age of 18 years – will develop a CUD.^{123,124}
 - Dispensary cannabinoid products available now are far more potent than those sold even a few years ago. Rates of CUD associated with use of potent dispensary cannabinoids may be as high as 30%.¹²⁵
 - CUDs are associated with an increased likelihood of developing other SUDs.¹²⁶
 - Cognitive and behavioral effects
 - Short-term adverse effects include deficits in attention, memory and learning. Chronic use of cannabinoids may cause permanent cognitive deficits.^{127,128}
 - Daily use or high doses of Δ^9 -tetrahydrocannabinol can cause anxiety, paranoia and psychosis. Chronic cannabis use is associated with an increased risk of developing schizophrenia.¹²⁹⁻¹³⁸
 - Cannabis use is associated with higher rates of depression, anxiety and suicidality.¹³⁹⁻¹⁴¹
 - Cardiovascular effects
 - Smoking or vaping cannabinoids increases the risk for stroke and heart disease.¹⁴²⁻¹⁴⁵
 - Pulmonary effects
 - Smoking or vaping cannabis in any form can harm lung tissues, scar small blood vessels and expose patients to many of the same toxins, irritants and carcinogens found in tobacco smoke.^{146,147}
 - Second-hand cannabis smoke is harmful to the health of exposed contacts, particularly children and adolescents.¹⁴⁸
 - Malignancy
 - Chronic cannabis use may increase the risks of testicular cancer and human papilloma virus (HPV)-related head and neck squamous cell carcinoma (HNSCC).^{149,150}
 - Studies suggest that chronic use of cannabis may complicate pain management.^{151,152}
- Pregnant or breastfeeding patients are strongly advised to avoid cannabis use due to known and unknown risks to the developing brain, potential birth defects, possible autism or spectrum disorders, future drug-seeking behavior and other behavioral abnormalities.¹⁵³
- Despite the cautions above, pharmacists may counsel their patients that many physicians, researchers, the American Medical Association and the organizations represented in CO's CURE advocate for better scientific research into the safety and efficacy of cannabinoids for pain management.

Appendix VI 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 little risk of overdose death, their opioid-sparing potential and analgesic efficacy are unproven. Two ecological studies raised the possibility that medical cannabis legalization might reduce the use of opioids and rates of overdose death; however, subsequent individual-level research has challenged this hypothesis and some states have seen rates of opioid-related harms increase after enactment of medical cannabis legislation.¹⁵⁴⁻¹⁵⁶

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.¹⁵⁷ Evidence regarding the efficacy of cannabinoids, including dispensary cannabis, for the management of acute pain is nonexistent.¹⁵² 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.¹⁵⁸⁻¹⁶⁰

Though cannabinoids have been studied for decades, the barriers to cannabinoid research are many. In particular, plant-derived cannabinoids in the United States are classified as Schedule I substances for which research is tightly regulated. Furthermore, the pharmacokinetics of these substances are complex and depend on the composition of the synthetic or herbal product and the route of administration. The chemical content of unprocessed botanical cannabis varies significantly;

there are more than 100 pharmacologically active cannabinoids, the most widely studied of which are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD). The remaining cannabinoids and terpenes contribute to the smell, taste, and possible pharmacologic effects of cannabis.¹⁶¹ 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.¹⁶² 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.”¹⁶³

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.^{158,159,164-167} The human endocannabinoid system is composed of the cannabinoid receptors CB1 and CB2 and the endogenous human cannabinoids N-arachidonylethanolamine (AEA), also known as anandamide, and 2-arachidonoylglycerol.¹⁶⁸ CB1 receptors are concentrated in presynaptic neurons in areas of the brain that regulate appetite, memory, fear and motor responses, as well as in the spinal cord, dorsal root ganglia, the GI tract, liver, fat cells and skeletal muscle, while CB2 receptors are primarily found in macrophages and tissues that modulate inflammation.^{139,169}

Both cannabinoid receptors and endocannabinoids are involved in the regulation of pain sensation, with modulatory actions at all stages of pain processing pathways.¹⁷⁰ 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.¹⁵⁹ Mu-opioid receptors and CB1 receptors are both found in the dorsal horn of the spinal cord at the first synaptic contact for peripheral

Appendix VI continued

nociceptive afferent neurons.^{171,172} 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.¹⁵⁸⁻¹⁶⁰

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 GRADE system) found moderate evidence of a 30% reduction in pain in patients using cannabinoids (29.0%) when compared with placebo groups (25.9%). The number needed to treat (NNT) to achieve a reduction in pain was 24. A 50% reduction in pain was reported by 18.2% of subjects in the cannabinoid groups compared to 14.4% in the placebo groups; however, these findings were statistically insignificant. The number needed to harm (NNH), notably, was 6. For comparison, the NNT for opioids is 4, and the NNH is 5. The authors note that the change in pain intensity seen with cannabinoids was equivalent to a 3-mm greater reduction on a 100 mm visual analogue scale when compared with placebo—well below the 30-mm threshold needed to represent a clinically significant difference. They acknowledge that their analysis is limited by the small sample sizes of the studies surveyed, with only 21 studies having more than 100 patients per treatment arm. They also note the short duration of most studies and observe that the efficacy of cannabinoids for pain appeared to wane over even a few days. The authors express concern that the short duration of most studies means that long-term adverse events, including the risk of iatrogenic dependence, cannabinoid tolerance, and cannabinoid withdrawal syndrome, was not assessed by their review. They conclude that, while cannabinoids show modest benefit for the treatment of some pain conditions, they are unlikely to be effective for the management of chronic noncancer pain given their high NNT and low NNH.¹⁷³

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.¹⁷⁴ A subsequent 2019 scoping review assessed data from 72 systematic reviews of medical cannabinoid use.¹⁷⁵ 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.¹⁷⁵ 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.¹⁷⁵ Until larger, more methodologically rigorous studies are conducted, the results of meta-analyses will be of limited value in guiding patients and clinicians.

Adverse Effects of Cannabinoids

Although the legalization of medical and recreational cannabis has likely led some patients to consider these compounds as generally safe, the studies discussed above note significant adverse effects with cannabinoid use, including dizziness, dry mouth, tachycardia, fatigue, somnolence, nausea, vomiting, disorientation, confusion, anxiety, cannabis hyperemesis syndrome, paranoia and hallucinations. A recent survey of Colorado EDs describes increased frequency of patient visits for significant cannabis-related adverse effects, including psychosis, suicidality, concomitant substance abuse, decrements in complex decision-making, motor vehicle collisions, cardiovascular and pulmonary complications, inadvertent pediatric exposures and hash-oil burn injuries (sustained when preparing drug concentrates). Contaminants found in cannabis can also expose users to infectious agents, heavy metals and pesticides.¹⁷⁶ A retrospective review of adolescent ED and urgent care visits found a significant increase in cannabis-associated visits.¹⁷⁷ Another retrospective review found significant increases in cannabis-related hospitalizations, ED visits and poison center calls in Colorado both after local medical marijuana policy liberalization and after local recreational legalization. Of note was the high prevalence of mental illness presenting patient visits with cannabis-related codes, an association that warrants further investigation.¹⁷⁸

While the long-term adverse effects of cannabinoids require further research, a number of studies have associated THC exposure with the later development of

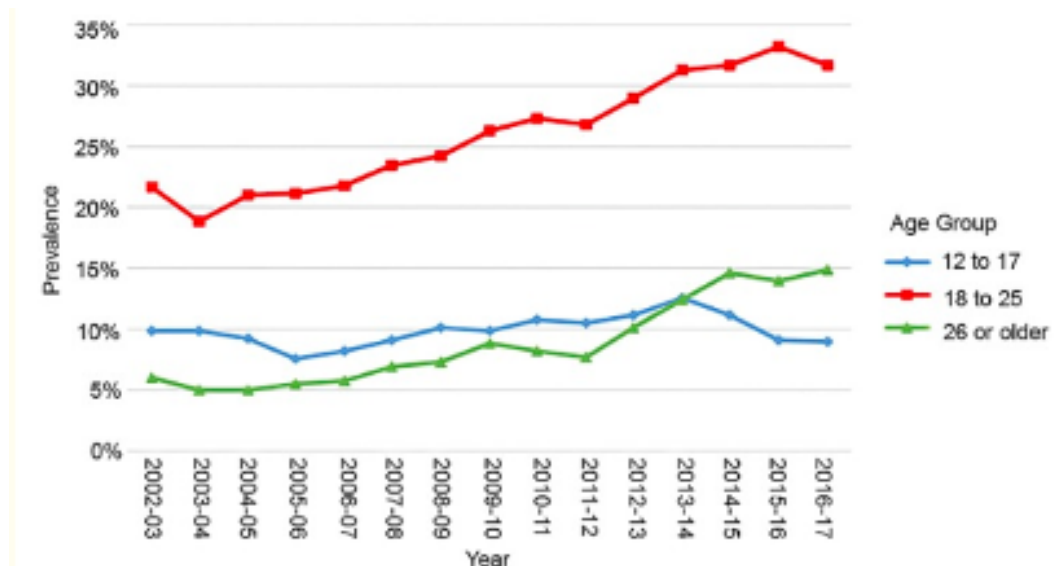
Appendix VI continued

schizophrenia,¹²⁹⁻¹³⁸ depression,^{140,142} anxiety¹³⁹ and suicidal ideation, attempts and completion.¹⁴¹ A large prospective cohort study also linked cannabis use to a substantial risk for the later development of CUD,¹⁷⁹ estimating that 9% of adults and 17% of adolescent users will develop the disorder.¹²³ Both grey- and white-matter changes have been found in chronic cannabis users, as have volume reductions in the amygdala and hippocampus.^{127,180-183} 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. An estimated 39% of patients who receive COT for pain report also using cannabis.^{184,185} 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 4)

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

Appendix XII

Additional Resources for OUD Assessment and Diagnosis

Diagnostic criteria for OUD from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013. (DSM-5).¹⁸⁶

- A checklist may be used for quick reference:
<https://www.asam.org/docs/default-source/education-docs/dsm-5-dx-oud-8-28-2017.pdf>

American Society of Addiction Medicine (ASAM, 2015) Recommendations for Assessment and Diagnosis.¹⁸⁷

- Assessment Recommendations
 - First clinical priority should be given to identifying and making appropriate referral for any urgent or emergent medical or psychiatric problem(s), including drug-related impairment or overdose.
 - Completion of the patient's medical history should include screening for concomitant medical conditions including infectious diseases (hepatitis, HIV and TB), acute trauma and pregnancy.
 - A physical examination should be completed as a component of the comprehensive assessment process. The prescriber (the clinician authorizing the use of a medication for the treatment of OUD) may conduct this physical examination themselves or, in accordance with the ASAM Standards, ensure that a current physical examination is contained within the patient medical record before a patient is started on a new medication for the treatment of their addiction.
 - Initial laboratory testing should include a complete blood count, liver function tests and tests for HCV and HIV. Testing for TB and sexually transmitted infections should also be considered. Hepatitis B vaccination should be offered, if appropriate.
 - The assessment of women presents special considerations regarding their reproductive health. Women of child-bearing age should be tested for pregnancy, and all women of childbearing potential and age should be queried regarding methods of contraception, given the increase in fertility that results from effective OUD treatment.
 - Patients being evaluated for addiction involving opioid use, and/or for possible medication use in the treatment of OUD, should undergo (or have completed) an assessment of mental health status and possible psychiatric disorders (as outlined in the ASAM Standards).
 - Opioid use is often co-occurring with other substance-related disorders. An evaluation of past and current substance use and a determination of the totality of substances that surround the addiction should be conducted.
 - The use of marijuana, stimulants or other addictive drugs should not be a reason to suspend OUD treatment. However, evidence demonstrates that patients who are actively using substances during OUD treatment have a poorer prognosis. The use of benzodiazepines and other sedative hypnotics may be a reason to suspend agonist treatment because of safety concerns related to respiratory depression.
 - A tobacco use query and counseling on cessation of tobacco products and electronic nicotine delivery devices should be completed routinely for all patients, including those who present for evaluation and treatment of OUD.
 - An assessment of social and environmental factors should be conducted (as outlined in the ASAM Standards to identify facilitators and barriers to addiction treatment, and specifically to pharmacotherapy). Before a decision is made to initiate a course of pharmacotherapy for the patient with OUD, the patient should receive a multidimensional assessment in fidelity with the ASAM Criteria. Addiction should be considered a bio-psycho-social-spiritual illness, for which the use of medication(s) is only one component of overall treatment.

Appendix VI continued

- Diagnosis Recommendations¹⁸⁷
 - Other clinicians may diagnose OUD, but confirmation of the diagnosis by the provider with prescribing authority and who recommends medication use must be obtained before pharmacotherapy for OUD commences.
 - OUD is primarily diagnosed on the basis of the history provided by the patient and a comprehensive assessment that includes a physical examination.
 - Validated clinical scales that measure withdrawal symptoms, for example, the Objective Opiate Withdrawal Scale, the Subjective Opiate Withdrawal Scale and the Clinical Opiate Withdrawal Scale, may be used to assist in the evaluation of patients with OUD.
 - Urine drug testing during the comprehensive assessment process, and frequently during treatment, is recommended. The frequency of drug testing is determined by a number of factors, including the stability of the patient, the type of treatment and the treatment setting.

Appendix XIII

Additional Resources for OUD Treatment

- American Society of Addiction Medicine – *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use* (ASAM, USA 2015)¹⁸⁷
 - This is a clinical treatment guideline developed for the evaluation and treatment of OUD for clinicians involved in evaluating patients and providing authorization for pharmacological treatments.
- Canadian Research Initiative in Substance Misuse – *National Guideline for the Clinical Management of Opioid Use Disorder* (CMAJ, 2018)¹⁸⁸
 - This is a Canadian treatment guideline for providers regarding the treatment of OUD. Its recommendations are primarily relevant to adults and young adults.
- Colorado Department of Regulatory Agencies – *Guidelines for the Safe Prescribing and Dispensing of Opioids* (DORA, 2019)¹⁸⁹
 - This brief document provides some considerations for all providers that prescribe, dispense and are otherwise a part of the treatment team for patients receiving or being considered for opioid therapy.
- Centers for Disease Control and Prevention – *CDC Guideline for Prescribing Opioids for Chronic Pain* – United States, 2016 (CDC, 2016)⁵⁷
 - This important national guidance document discusses relevant risk factors contributing to the development of OUD and subsequent risk for overdose in the context of the treatment of chronic pain.
- Substance Abuse and Mental Health Services Administration – *TIP 63: Medications for Opioid Use Disorder, Part 3: Pharmacotherapy for Opioid Use Disorder*¹⁹⁰
 - Part 3 of 5 describes the general principles of OUD pharmacotherapy and provides specific information about the use of methadone, naltrexone and buprenorphine.

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