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

Obstetrics and Gynecology

2020 Opioid Prescribing and Treatment Guidelines

Developed by the Colorado Section of the American College of Obstetricians and Gynecologists in partnership with Colorado Hospital Association, Colorado Medical Society and Colorado Consortium for Prescription Drug Abuse Prevention

COLORADO MEDICAL SOCIETY

COLORADO CONSORTIUM for Prescription Drug Abuse Prevention

c|h|a Colorado Hospital Association

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.

SPONSORING ORGANIZATIONS

c|h|a Colorado Hospital Association

COLORADO MEDICAL SOCIETY

COLORADO CONSORTIUM for Prescription Drug Abuse Prevention

PARTICIPATING ORGANIZATIONS

shm Society of Hospital Medicine Rocky Mountain Chapter

CDA COLORADO DENTAL ASSOCIATION

Colorado Chapter of the American College of Surgeons

CPS COLORADO PAIN SOCIETY

ARTS Addiction Research & Treatment Services

COLORADO CHAPTER American College of Emergency Physicians ADVANCING EMERGENCY CARE

ACOG The American College of Obstetricians and Gynecologists

COSAM Colorado Society of Addiction Medicine

Colorado Psychiatric Society

COLORADO PHARMACISTS SOCIETY

Rocky Mountain Urological Society, Inc.

CSA Colorado Society of Anesthesiologists

Rocky Mountain Academy of Occupational and Environmental Medicine, Inc.

FUNDED BY

Colorado Department of Human Services, Office of Behavioral Health

SPECIAL THANKS TO

Support for Hospital Opioid Use Treatment (Project SHOUT) and BridgetoTreatment.org

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

Contributors

Editors-in-Chief

Elizabeth Esty, MD
Donald E. Stader III, MD, FACEP

Obstetric and Gynecologic Specialty Editors

Amy Adelberg, MD
Julie C. Gelman, MD, FACOG
Jill H. Liss, MD, FACOG
Brandi N. Ring, MD, FACOG, FAWM
Maridee D. Shogren, DNP, CNM, CLC
Marcela C. Smid, MD, MA, MS, FACOG, FASAM
Mishka Terplan, MD, MPH, FACOG, DFASAM
Cristina Wood, MD, MS

Associate Editors

Brian T. Bateman, MD, MSc
Jonathan Clapp, MD
Rachael Rzasa Lynn, MD
Steven G. Young, MD, FASAM

Section Editors

Robert Valuck, PhD, RPh, FNAP
Introduction: The Opioid Epidemic
Elizabeth Esty, MD
Limiting Opioid Use in Obstetric and Gynecologic Practice
Rachael Duncan, PharmD, BCPS, BCCCP
Rachael Rzasa Lynn, MD
Cristina Wood, MD, MS
Multimodal Analgesia in Obstetric and Gynecologic Practice
Martin Krsak, MD
Donald E. Stader III, MD, FACEP
Harm Reduction
Elizabeth Esty, MD
Mishka Terplan, MD, MPH, FACOG, DFASAM
Steven G. Young, MD, FASAM
Treatment of Opioid Use Disorder
Debra Parsons, MD, FACP
Donald E. Stader III, MD, FACEP
Darlene Tad-y, MD, SFHM
Robert Valuck, PhD, RPh, FNAP
The Future and Ending the Opioid Epidemic in Colorado

Contributing Editors

Julie Denning
Nathan Novotny
John Spartz
Ryan Rotanz Tsipis, MPH
Helena Winston, MD
Narin Wongngamnit, MD

Task Force Members and Volunteers

Kevin Boehnke, PhD
Kenneth Finn, MD
Indra Wood Lusero, Esq, MA

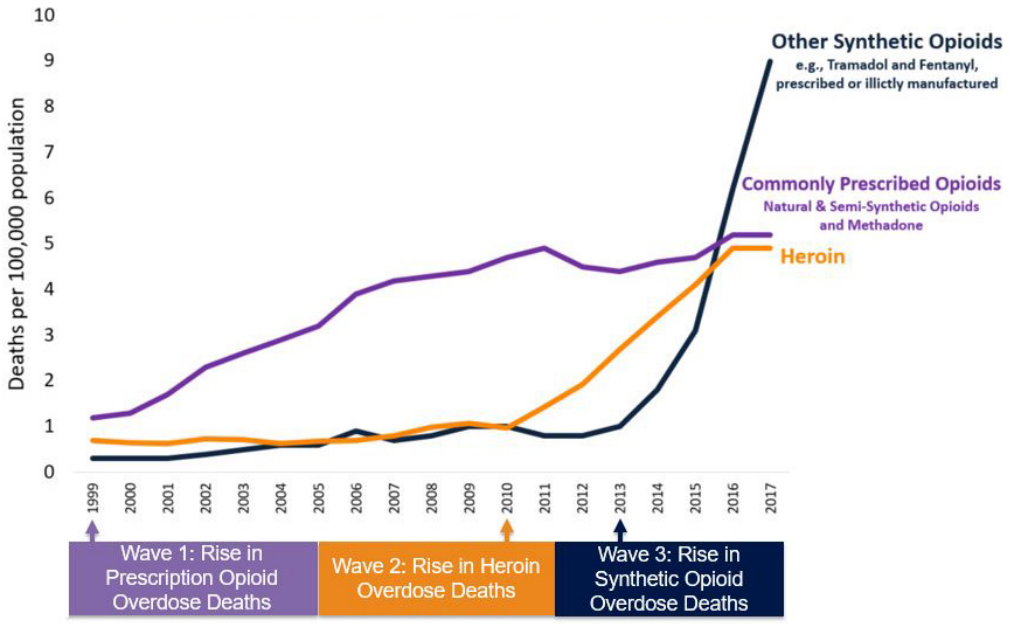
Table of Contents

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 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 2000 and 2017, and currently an average of 130 Americans die every day of opioid overdose **(FIGURE 1)**.[2,3]

(FIGURE 1)

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



SOURCE: CDC MMWR[3]

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.[4] The pharmaceutical use of opioids skyrocketed between 1990 and 1996: prescriptions for fentanyl rose 1,000%, followed by morphine (49%), oxycodone (15%) and hydromorphone (12%).[5] The number of prescription opioids sold in the United States increased five-fold between 1999 and 2017, and prescription opioids were involved in 218,000 overdose deaths 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.[6]

The dire consequences of the widespread availability of prescription opioids emerged over time. The "lag period" between a patient's first exposure to an opioid (either medical or nonmedical) and their first treatment admission is an average of seven years. For patients who die of an overdose, the time between their first exposure to an opioid and death is between nine and 13 years.[7,8] In 2017, opioids were responsible for 34% of all substance use disorder (SUD) treatment admissions for patients aged 12 years and older.[9] The economic implications of this epidemic are staggering; the White House Council of Economic Advisers estimates that the full economic cost of the opioid epidemic was $696 billion in 2018, a figure that represents 3.4% of the gross domestic product of the United States.[10]

While a number of external factors have contributed to the liberal use of these potentially lethal drugs, the medical community is compelled to acknowledge its role in creating this crisis. Fortunately, clinicians and health care systems also have the power to reverse these grim statistics by reforming their practices with resolve and innovation.

Introduction continued

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.[12-15] 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.[16] As a result, many pharmaceutical companies began to aggressively market their opioids for wider use at increased dosages and in extended-release formulations.

Beginning in the 1990s, medical providers were taught that oligoanalgesia was morally reprehensible—a rampant problem that could be solved by more liberal prescribing of opioids. The rising popularity of patient satisfaction surveys and similar ideologies further fueled this campaign, resulting in a 400% rise in U.S. opioid sales from 1999 to 2014.[17] Once reserved for only the most severe pain, these agents quickly became routinely prescribed. The current epidemic of OUD and overdose death is in large part a consequence of changes in physician prescribing patterns.

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.

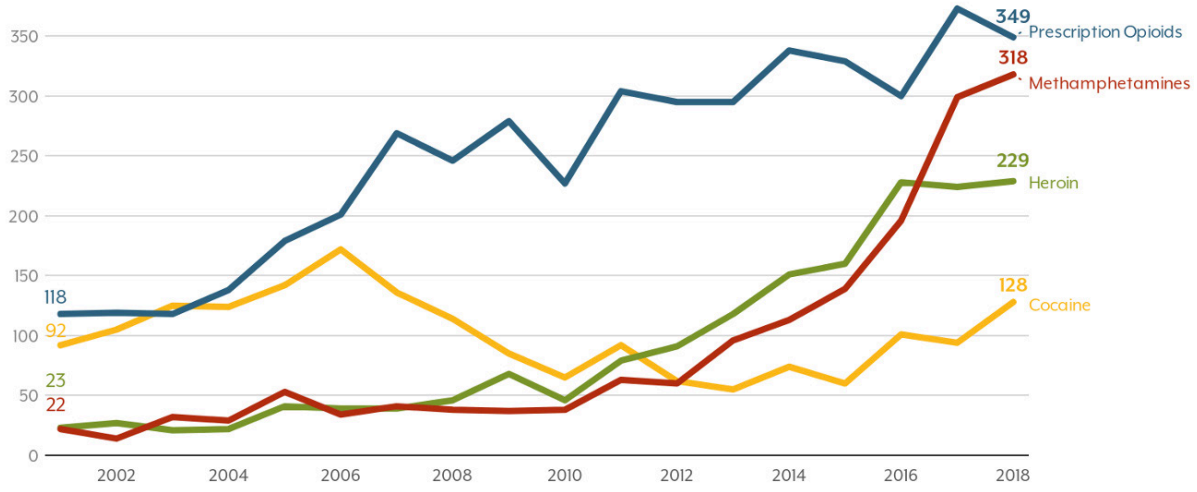
The Opioid Epidemic in Colorado

Coloradans have been significantly affected by this national public health crisis. Since 2000, Colorado has seen 6,030 overdose deaths from opioids.[21] There were a total of 1,635 prescription opioid-related overdose deaths in Colorado from 2013 to 2017, translating to a rate of 5.8 deaths per 100,000 Colorado residents.[22] Heroin-related opioid overdose deaths have increased 76% from 2013 to 2017.[22]

Introduction continued

(TABLE 1)

Poisoning Deaths by Substance in Colorado, 2002-2018



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

Chart: Colorado Health Institute · Source: Colorado Department of Public Health and Environment

SOURCE: Colorado Health Institute[23]

Colorado Statistics

While opioid prescribing rates and rates of high-risk prescribing in Colorado have declined, rates of overdose death remain unacceptably high. As noted above, the development of OUD lags behind initial exposure to an opioid, and thus the impact of reduction in opioid prescribing may not be evident for years. While rates of prescription opioid overdose are higher in males than females, from 1999 to 2016 rates of death from prescription opioid overdoses increased more rapidly for women (596%) than for men (312%). Women between the ages of 45 and 54 are more likely than women of other age groups to die from a prescription opioid overdose.[24]

In 2017 in the state of Colorado:

- More than 3.7 million opioid prescriptions were dispensed to one million patients at retail pharmacies **(TABLE 2)**. These numbers fell slightly from a high of 4.3 million opioid prescriptions for 1.1 million patients in 2015.[22]
- There were 1,012 drug overdose deaths, 57% of which involved an opioid.[22]
- Fifteen percent of opioid-naive patients were prescribed long-acting opioids.[25]
- Ten percent of patient prescription days involved overlapping opioid and benzodiazepine prescription use.[25]
- There were 671.3 opioid prescriptions filled per 1,000 residents.[25]
- 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]
- According to the Colorado Department of Public Health and Environment (CDPHE), 22% of all scheduled medications prescribed in Colorado were dispensed to women between the ages of 15-44. A majority of these prescriptions were for opioids (49%), followed by benzodiazepines (23%) and stimulants (21%), and 5.3% of women prescribed an opioid were prescribed more than the CDC recommended 90 milligram morphine equivalents (MME).

Introduction continued

(TABLE 2)

Characteristics of Opioid Prescriptions Dispensed, Colorado 2014-2017

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

Excludes buprenorphine drugs commonly used to treat opioid use disorder
In 2014 NPI was used to identify unique prescribers and pharmacies as DEA numbers were not available until 2015
Data Source: Colorado Prescription Drug Monitoring Program, Colorado Department of Regulatory Agencies Analysis by: Colorado Department of Public Health and Environment, 2018

SOURCE: Colorado Opioid Profile[22]

(TABLE 3)

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

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

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

SOURCE: Colorado Opioid Profile[22]

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, health care practitioners and hospitals must work together to turn the tide and resolve the crisis.

Introduction continued

CO's CURE

Faced with the greatest public health crisis of a generation, Colorado is taking a stand for the benefit of all. CO's CURE is the nation's first set of comprehensive, multispecialty medical guidelines designed to end the opioid epidemic. 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 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 hospitals and clinicians to aid in the prevention of opioid misuse and addiction and the identification, treatment and support of patients with OUD. It is unlikely that a hospital or obstetric-gynecologic practice can or will attempt to implement each strategy or idea included in these guidelines. Rather, hospitals 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.

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.

NOTE: These guidelines strive to be inclusive of all obstetric and gynecologic patients. "They/them" pronouns are used throughout. While the term "woman" also appears, the CO's CURE editors and the Colorado section of the American College of Obstetricians and Gynecologists (ACOG) recognize that this term may not encompass all individuals seeking obstetrician-gynecologist care, including those who identify as transgender, nonbinary and gender-fluid.

Limiting Opioid Use in Obstetric and Gynecologic Practice

c|h|a
Colorado Hospital Association

COLORADO
MEDICAL SOCIETY

COLORADO
CONSORTIUM
for Prescription Drug Abuse Prevention

Limiting Opioid Use in Obstetric and Gynecologic Practice

The majority of patients who become addicted to opioids, both prescription and illicit, received their first dose directly or indirectly from a physician. It is clear that many factors contribute to the development of OUD in an individual patient, and it is worth noting that the vast majority of individuals prescribed an opioid by an obstetrician-gynecologist do not go on to develop OUD. Genetic factors, environmental stressors (both present and past) and behavioral health comorbidities contribute to risk. Screening for risk factors for addiction may identify patients for whom limiting or avoiding opioid exposure is vital. Unfortunately, screening is an imperfect tool, and it is prudent to view every patient as being at some risk for addiction.

One clear way to reduce the likelihood of opioid misuse, addiction and overdose death is to reduce the prescription of opioids. Women are more likely to experience both acute and chronic pain, be prescribed opioids and be prescribed higher doses and longer courses of opioids than men.[26-28] At the same time, evidence suggests that women may become dependent after shorter durations and at lower doses of substance exposure than men.[29] One large study found that of opioid-naive patients prescribed at least one day of an opioid, 6% became long-term users; for those whose first prescription was for >8 days, the rate increased to 13.5%; and for those prescribed a >30-day supply of opioids, 29.9% became long-term users.[30] Similarly, chronic opioid use after surgery occurs at astonishingly high rates, with one study finding that 5.9% of opioid-naive patients undergoing minor procedures and 6.5% of patients undergoing major surgeries will go on to become chronic opioid users.[31,32] While one study of opioid-naive patients undergoing hysterectomy found that only 0.5% of patients went on to persistent use following surgery, given that more than 400,000 individuals undergo the procedure every year, this still represents a significant number of patients.[33] Two large studies find rates of new persistent opioid use following cesarean delivery of 0.33% and 2.2%.[34,35] Even if only one in 300 opioid-naive patients progress to persistent opioid use after cesarean delivery, because more than 1.2 million people in the United States undergo the procedure every year, that small fraction represents many thousands of individuals.[34]

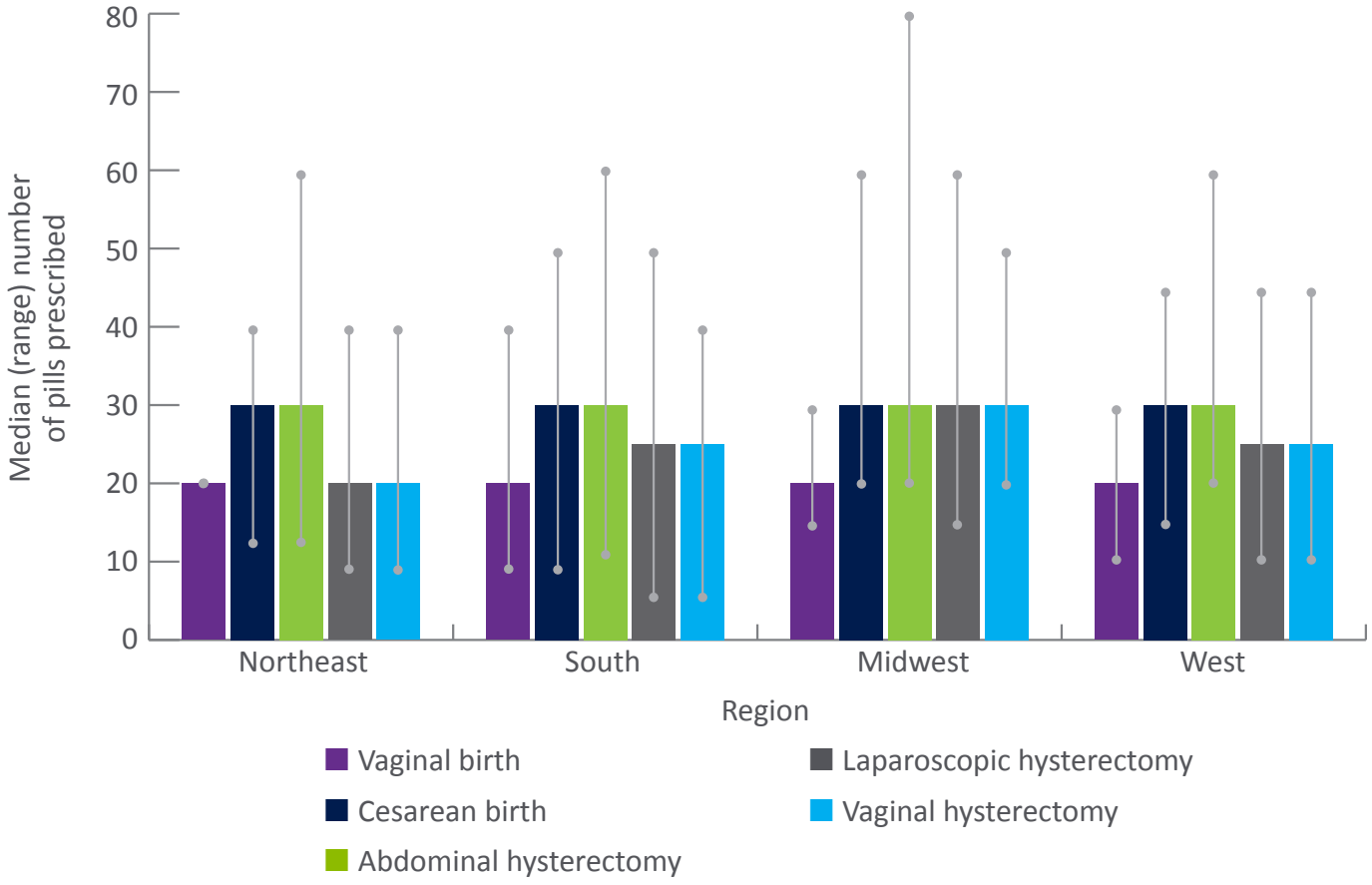
A large body of research demonstrates that, on average, patients are prescribed more opioids than they report using and that a small fraction of obstetrician-gynecologists prescribe many times the quantity of opioids their patients actually need **(FIGURE 2)**.[34,36-44] Opioid analgesia has been a mainstay of perioperative pain management and the treatment of pain in a range of nonoperative gynecologic disorders. The current epidemic of OUD and overdose death, however, underscores the importance of thoughtful opioid ordering and prescribing, the impact on patients and communities, and the need for additional education on OUD.

Over-prescription of opioids poses risks not only to patients, but to families and communities as well. More than 90% of surgical patients fail to dispose of unused opioids and thus contribute to a vast reservoir of opioids available for diversion; few patients keep unused opioids in a locked location.[41,45] Awareness and education about OUD has not been a priority in medical education. A recent survey of obstetrician-gynecologists found that 81% incorrectly identified the main source of misused opioids—diversion from a friend or family member—and 44% did not know how to properly dispose of unused prescription opioids.[36]

Limiting Opioid Use in Obstetric and Gynecologic Practice continued

(FIGURE 2)

Median and Range of Opioid Pills Prescribed by Region for Various Procedures



SOURCE: Madsen, Opioid Knowledge and Prescribing Practices Among Obstetrician-Gynecologists Obstetrics & Gynecology[36]

Clinicians rely on prescribing patterns learned in training from previous generations that are not always evidence-based best practices. By reducing their reliance on opioid analgesia and leveraging the wide array of alternative pain management tools now available, obstetrician-gynecologists can be part of the solution to the opioid epidemic. Across all specialties, a commonsense first step to addressing the epidemic of OUD is to decrease the frequency and ease with which opioids are dispensed. Obstetrician-gynecologists can play a vital role in screening patients, using alternative analgesics, prescribing opioids conservatively, and providing thorough counsel on the risks of addiction and diversion prior to discharge including safe disposal of unused opioids.

Practice Recommendations to Reduce the Risks Associated with Opioid Therapy

If the decision to use an opioid is made in office practice, perioperatively or in the peripartum period, consider following these practice recommendations to reduce the risk of adverse effects of opioid therapy. (Recommendations may not apply to patients receiving ongoing opioid therapy for chronic pain or treatment of OUD.)

1. **Opioids are inherently dangerous drugs with significant potential for misuse and addiction, numerous side effects, rapid development of tolerance, debilitating withdrawal symptoms and lethality in overdose. Obstetrician-gynecologists are advised to limit their use of opioids to patients with severe or moderate pain that has not responded or is not anticipated to respond to nonopioid multimodal analgesia.**
   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.[46,47] This mechanism also contributes to the high risk of overdose following a period of abstinence.[48] Tolerance can be lost in times of abstinence, and a return to use at a previously "safe" dose can result in overdose.[49]
   c. Opioid therapy is associated with a number of common, sometimes serious side effects, including sedation, respiratory depression, constipation, nausea and vomiting, impaired judgment and coma **(TABLE 4)**.[50-52]
   d. 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.[53-63]
   e. 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 remifentanil, may produce OIH.[64,65]
   f. Genetic variation, particularly in the cytochrome P450 2D6 (CYP2D6) enzyme, creates significant patient variability in the metabolism of many opioids. This variability leads to increased rates of ORADEs for some patients and undertreatment of pain for others.[66-68]
   g. Given these risks associated with opioid use, the risk-to-benefit ratio does not support the use of opioids in low-severity pain level management if nonopioid alternatives are viable options. Opioids are best reserved for pain that is severe or limits function despite the use of nonopioid treatments.

(TABLE 4)

Adverse Effects of Opioids

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

SOURCE: Martin PR, Hubbard JR. Substance-related disorders. In: Ebert MH, Loosen PT, Nurcombe B: Current Diagnosis & Treatment in Psychiatry. New York: McGraw Hill; 2000:233-259.[52]

2. Obstetrician-gynecologists are encouraged to work with patients to establish realistic goals and expectations for management of pain.

a. Obstetrician-gynecologists are encouraged to provide patients, families and caregivers with educational resources about their condition and treatment, and the role of opioids in analgesia. Patient education can improve both health outcomes and the patient experience.[69,70]

b. Patients should be aware that the goal is not necessarily to be pain free, but to have pain at a manageable level. Discussions regarding the expected course of recovery ideally include that acute pain is expected to resolve as the underlying condition improves and/or as surgical healing occurs.

c. It is suggested that obstetrician-gynecologists educate patients, families and caregivers on the normal physiology of postoperative healing and emphasize that a period of rest and limited work and social responsibilities may accelerate healing and recovery after surgery. In addition, patients may be advised that overtreatment of pain may mask early indications of a surgical complication.

d. Clinicians are encouraged to educate patients and caregivers that improvement is best defined by recovery of function rather than by scores on numerical pain scales. It is important to explain that improvement in pain without improvement in function is not considered meaningful improvement in most cases and should prompt reevaluation of the diagnosis and the appropriateness of therapy.

e. For all patients, it is recommended that maximal use of nonopioid analgesics and nonpharmacologic pain management and the appropriate cessation of opioids be a common goal for the patient and the treatment team.

Limiting Opioid Use in Obstetric and Gynecologic Practice continued

3. **Opioids are not recommended as first-line analgesic therapy for the treatment of the following conditions: chronic pelvic pain, endometriosis, dysmenorrhea, dyspareunia, ovarian cysts, vulvodynia, miscarriage and pain during and after uncomplicated vaginal delivery.**
   a. A recent national survey of American College of Obstetricians and Gynecologists fellows and junior fellows found that 30% of providers reported routinely prescribing opioids for ovarian cysts, 24% for endometriosis and 18% for chronic pelvic pain of unknown cause.[36]
   b. A retrospective cohort study of 308,226 deliveries by opioid-naive women in the United States between 2008 and 2016 found that 27% of women filled a prescription for an opioid after a vaginal delivery. Of these, 1.7% went on to develop new persistent opioid use, compared to 0.5% of women not prescribed an opioid.[35] An ACOG postpartum pain management committee opinion recommends use of nonopioid multimodal analgesia prior to prescription of an opioid and advises use of the lowest effective opioid dose.[71]
   c. Per ACOG Practice Bulletin 218, opioids are not recommended for the treatment of chronic pelvic pain.[72]
   d. ACOG recommends that adolescents not be prescribed opioids long term to manage endometriosis outside of a specialized pain management plan.[73]
   e. **SEE SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE**, for nonopioid analgesic interventions that may be of benefit to patients with common painful gynecologic conditions and patients with uncomplicated vaginal delivery.

4. **Obstetrician-gynecologists are encouraged to educate patients about the potential risks and side effects of opioid therapy as well as the availability of alternative pharmacologic and nonpharmacologic therapies for managing pain.**
   a. Patients are often not aware of the short- and long-term risks associated with opioid medications or that there may be equally effective pharmacologic and nonpharmacologic alternatives to opioids available for the treatment of pain.
   b. Fewer than one in five Americans consider prescription pain medication to be a serious safety threat. Evidence suggests that clinicians do a poor job of educating patients on the risks of opioids.
   c. When prescribing opioids, it is always appropriate to initiate a detailed discussion about the significant risk of immediate adverse effects and the longer-term risks of dependence and addiction. Obstetrician-gynecologists are encouraged to explain to patients that opioids may impede recovery from surgery or disease via respiratory suppression, contributing to hypoxia and/or atelectasis; sedation, impairing ambulation and nutrition; ileus and constipation, slowing return to normal GI function; nausea and vomiting; and impaired immune response.
   d. The National Safety Council estimates that more than half of U.S. patients have at least one risk factor for the development of OUD.[74] A personal or family history of SUD, current alcohol or tobacco use, chronic pain and behavioral health disorders all increase this potential; however, patients should be aware that an opioid-naive patient with no risk factors can develop OUD.[75,76]
   e. Obstetrician-gynecologists are encouraged to inform patients that they may request nonopioid multimodal analgesia in lieu of opioids, even for severe postoperative pain.

5. **Prior to prescribing an opioid, obstetrician-gynecologists are encouraged to review the information contained in the Colorado Prescription Drug Monitoring Program (PDMP) to inform decision-making around opioid therapy.**
   a. The Drug Enforcement Administration (DEA) requires all practicing physicians to create an account with the Colorado PDMP.[77] Colorado House Bill (HB) 14-1283 requires all Colorado-licensed prescribing practitioners with DEA registrations to create an account with the Colorado PDMP.[78]
   b. Drug monitoring programs have been shown to influence opioid prescribing practices, especially in the case of lost or long-term prescriptions.[77] These programs can aid providers in identifying patients with multiple recent prescriptions from multiple providers and help identify those already using other controlled medications on a chronic basis.[79]
   c. Although there is limited data to indicate the impact of PDMPs on patient outcomes, these programs can prompt referral to support services, initiation of medication for addiction treatment (MAT) and/or consultation with a pain management or addiction specialist.
   d. Along with information gathered from PDMPs, concerns about possible misuse of controlled substances or the presence of SUD can prompt further conversations between physician and patient.
   e. Information from PDMPs does not preclude the use of opioids for treatment of acute or chronic pain but can be incorporated into the analysis of the risks and benefits of opioid therapy.
   f. Colorado Senate Bill (SB) 18-022, Clinical Practice for Opioid Prescribing, limits first-time opioid prescriptions for acute noncancer pain to seven days, with the ability to add a discretionary second seven-day refill.[80] Prescribers must check the PDMP prior to prescribing a subsequent fill of an opioid.[80] The bill outlines exceptions to this seven-day limit, including postsurgical pain that is expected to last more than 14 days. It is recommended that providers not refuse to provide appropriate care to patients who require opioid analgesia out of misconceptions of Colorado law.
   g. Acute pain lasting longer than seven days after the appropriate treatment of any existing underlying conditions may prompt reevaluation of the working diagnosis and/or management approach. To prescribe further opioids to the same patient, clinicians are required per Colorado SB 18-022 to review the PDMP.[80]

6. **Obstetrician-gynecologists are advised to use the lowest effective opioid dose for the shortest possible duration to manage pain in the outpatient, inpatient, peripartum and perioperative settings. For acute pain, a one- to three-day supply of opioid analgesics is usually adequate.**
   a. There is evidence that higher doses of opioid therapy are associated with higher incidence of ORADEs, particularly overdose, in both inpatient and outpatient settings.[81,82]
   b. In a study of 1,294,247 opioid-naive patients prescribed an opioid for acute pain, the rate of long-term opioid use rose with every additional day of opioid use, with a rate of chronic opioid use of 6% for those receiving a prescription for at least one day of opioids, 13.5% for patients with a first episode of use of ≥ 8 days and 29.9% if the first episode of use was ≥ 31 days.[30] The same study found that refilling a prescription for an opioid was associated with a one in seven chance of persistent opioid use one year later.[30] In addition, prescribing more than 700 MME is associated with an increased risk of chronic opioid use.[30]
   c. It is recommended that the need for opioids be reassessed frequently in both inpatient and outpatient settings to adjust dosage in accordance with healing, pain improvement and functional improvement.
   d. Evidence suggests that clinicians may prescribe far fewer opioids (or no opioids) without jeopardizing analgesia or patient satisfaction.[83]
   e. When opioid analgesia is used, the concurrent administration of nonopioid analgesics can reduce the patient's total opioid requirements and improve pain management.[84]
   f. It is suggested that computerized physician order sets default to the lowest possible dosage of opioid and that dosing be on an as-needed rather than scheduled basis.

7. If an opioid is required, obstetrician-gynecologists are encouraged to use immediate-release monoproduct opioid formulations and avoid initiation of long-acting or extended-release formulations for treatment of acute pain, postoperative pain and postpartum pain.

a. Long-acting or extended-release opioids are indicated only for the treatment of chronic pain, OUD or opioid withdrawal. They are not recommended for the treatment of acute or intermittent symptoms.[85]

b. Long-acting and extended-release agents are especially dangerous in opioid-naive patients, even at recommended dosages, and are associated with an increased risk of overdose.[86] Long-acting and extended-release opioids carry a long-term risk of dependence that is nearly 4.5 times higher than that seen with immediate-release formulations.[30]

c. For patients taking long-acting or extended-release formulations for the treatment of addiction or chronic pain, the discontinuation of these agents is discouraged; opioids are generally necessary to meet the baseline requirements of these patients. (For guidance **SEE "MANAGING PERIOPERATIVE PAIN IN GYNECOLOGIC PATIENTS RECEIVING MAT" IN SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE.**)

d. Opioid products with a single ingredient (e.g., oxycodone) are favored over combination formulations (e.g., oxycodone/acetaminophen), as patients are encouraged to take nonopioid analgesics (e.g., acetaminophen, nonsteroidal anti-inflammatory drug [NSAID]) consistently prior to resorting to an opioid. Use of monoproducts allows acetaminophen or NSAID to be taken preferentially and used as a first-line agent with a lower risk of supratherapeutic dosing or accidental poisoning.

(TABLE 5)

Commonly Prescribed Opioids

Short-acting opioids include but are not limited to the following agents:[87-89]

- Hydrocodone — immediate release (e.g., Vicodin,* Lorcet,* Lortab,* Norco*)
- Hydromorphone — immediate release (e.g., Dilaudid)
- Morphine — immediate release
- Oxycodone — immediate release (e.g., Percocet,* Percodan,* Roxicodone)
- Oxymorphone — immediate release (e.g., Opana)
- Tramadol — immediate release (e.g., Ultracet,* Ultram); *note caution regarding tramadol in this section*
- Tapentadol — immediate release (e.g., Nucynta)

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

- Fentanyl — transdermal (e.g., Duragesic)
- Hydrocodone — extended release (e.g., Hysingla ER, Zohydro ER)
- Hydromorphone — extended release (e.g., Exalgo)
- Methadone (e.g., Dolophine)
- Morphine — sustained release (e.g., MS Contin, Avinza, Kadian)
- Oxycodone — sustained release (e.g., OxyContin, Xtampza ER)
- Oxymorphone — extended release (e.g., Opana ER)
- Tramadol — extended release (e.g., Ultram ER); *note caution regarding tramadol in this section*
- Tapentadol — extended release (e.g., Nucynta ER)

** denotes combination product*

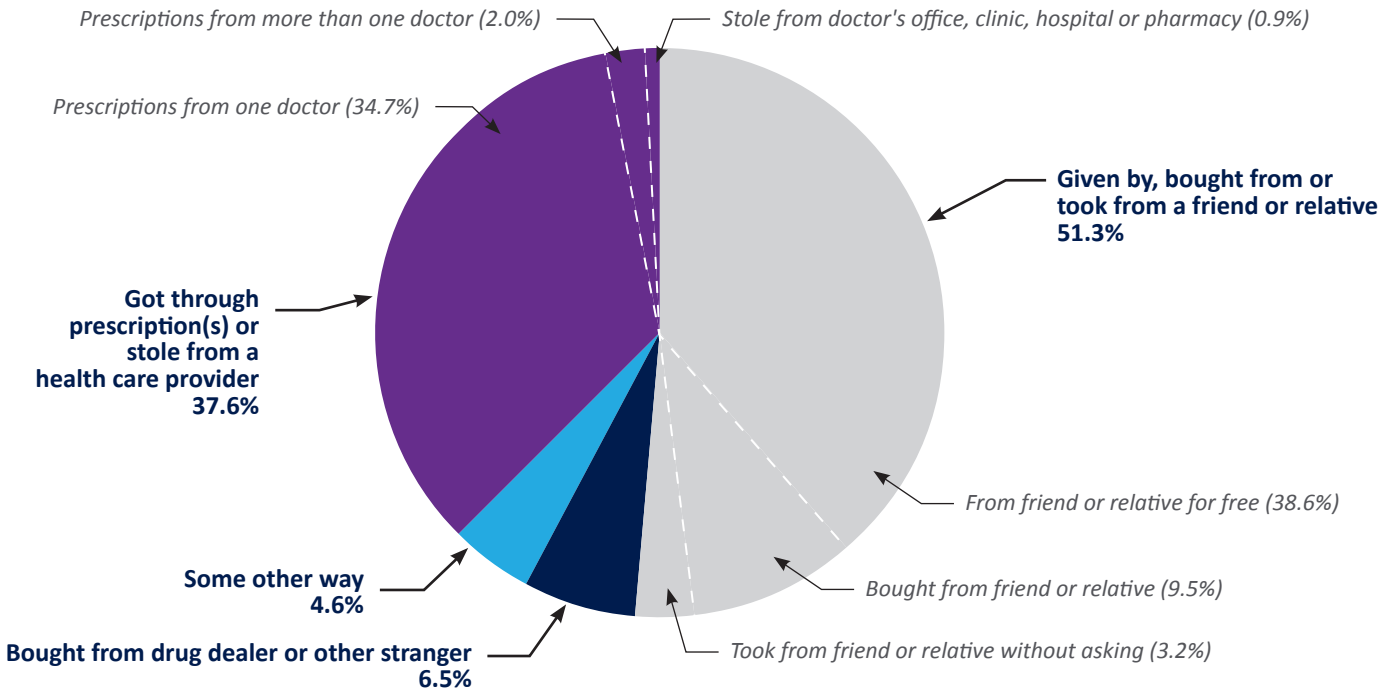
8. **Understand that tramadol is not a "safe" opioid. The drug carries significant side effects and has been associated with significant rates of long-term opioid use.**
   a. Tramadol binds weakly to u-opioid receptors after undergoing conversion to its active metabolite O-desmethyltramadol by CYP2D6. The drug also has serotonin-norepinephrine reuptake inhibitor (SNRI) activity among several other mechanisms of action. Wide variations in the pharmacogenetics of tramadol metabolism can result in significant individual differences in concentrations and analgesic effect.[90]
   b. Widely viewed as a "less potent" opioid, clinicians often prescribe tramadol for acute pain in an attempt to avoid "stronger" medications. Tramadol is a Schedule IV drug, a factor that may reinforce this assumption. Unfortunately, not only does tramadol carry additional side effects, including seizures and significant drug interactions not seen with other opioids, the medication also appears to pose a significantly greater risk of long-term opioid use.
      i. Tramadol has been associated with an elevated risk of long-term opioid use at one and three years compared to other opioids.[30] Significantly higher rates of long-term opioid use were found in a cohort of opioid-naive patients receiving tramadol after elective surgery compared to those prescribed other short-acting opioids.[91]
      ii. Additional studies have identified higher rates of adverse events, including overdose, among adolescents taking tramadol.[92]

9. **It is recommended that obstetrician-gynecologists avoid, or limit if avoidance is not possible, prescription or co-administration of opioids with barbiturates, benzodiazepines, gabapentinoids and other CNS depressants.**
   a. This combination has been demonstrated to increase the risk of ORADEs in multiple settings of care, including during hospitalization.
   b. Patients taking opioids and benzodiazepines together have 10 times the risk of fatal overdose of those taking opioids alone.[93]
   c. Other medications with CNS depressant properties may also increase the risk of overdose, including but not limited to non-benzodiazepine sedative-hypnotics, gabapentinoids, muscle relaxants, sedating antidepressants, antipsychotics and antihistamines.[82,94,95]
   d. Routine discontinuation of long-standing benzodiazepines, barbiturates and other CNS depressants is not advised due to the risk of withdrawal or worsening of the underlying condition for which these agents were prescribed. This can pose a dilemma for a clinician who must order concurrent opioid therapy to control pain. In these cases, clinicians may wish to carefully consider the necessity of each medication class with input from the patient's other providers. Clinicians are encouraged to taper the frequency and/or dose of CNS depressants when appropriate and feasible, utilizing the knowledge and assistance of a pharmacist as needed and to avoid new co-prescriptions to the extent possible.

10. **It is recommended that all patients who receive prescriptions for opioids be educated on the dangers that unsecured opioids pose to others and in the safe storage and proper disposal of unused medications.**
    a. More than 50% of nonmedical opioid users obtain their medication from family members or friends.[96-98] The CDC recommends that prescribers discuss the risks that shared and diverted opioids pose to household members and other individuals. In particular, it is important to emphasize the possibility that others might experience overdose at the same or a lower dosage than was prescribed for the patient. Nearly all opioid exposures in children are from medications prescribed to an adult in the household.[42,99] One study determined that children of women prescribed opioids have a 2.4-fold increase in risk for opioid overdose.[100] The diversion of opioids by adolescents also poses a significant risk.[101]

(FIGURE 3)

Where Pain Relievers Were Obtained for Most Recent Misuse among People Aged 12 or Older Who Misused Pain Relievers in the Past Year: 2018



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

NOTE: Respondents with unknown data for the source for most recent misuse or who reported some other way but did not specify a valid way were excluded.

SOURCE: SAMHSA NSDUH 2018[102]

b. It is recommended that prescriptions be stored safely, ideally in a locked location. More than three-quarters of individuals store their opioid medications in unlocked locations.[102]
c. A cross-sectional survey of patients prescribed an opioid for either chronic or acute pain found that only one-third of patients reported receiving information from their health care provider on safe storage (35.2%) and/or disposal (31.4%) of their opioids and that half received neither storage nor disposal information.[103]
d. Obstetrician-gynecologists are encouraged to inquire about unused opioids at postoperative office visits. Studies show that between 67-92% of patients have unused opioids after surgery, but fewer than 10% actually dispose of their unused medications.[45]

e. It is critical to dispose of unused medication promptly. If disposing of medication at home, it is advised that patients be instructed to:
   i. Remove the medication from its original container and remove any labels and identifying information.
   ii. Mix the pills with something inedible (e.g., kitty litter, coffee grounds, sawdust, home cleanser, etc.).
   iii. Place the mixture in a sealable bag, empty can or other durable container that prevents leakage.
   iv. Wrap the container in newspaper or a plain brown bag to conceal its contents. Place it in a trash can on the day of collection.
   v. The U.S. Food and Drug Administration (FDA) allows opioids to be flushed down a toilet; however, more environmentally friendly disposal methods are encouraged.[104]

f. An increasing number of communities offer prescription take-back programs. It is advised that patients use one of the preferred disposal locations found using the resources listed below. More than 50% of Colorado counties provide safe disposal sites for controlled substances, and the number of these facilities is rapidly increasing. Safe disposal resources include:
   i. http://www.takemedsseriously.org
   ii. http://www.corxconsortium.org/wp-content/uploads/Safe-Disposal-Brochure.pdf
   iii. http://www.deadiversion.usdoj.gov/drug_disposal/takeback/index.html

11. It is suggested that obstetrician-gynecologists use an opioid equivalency table or calculator to understand the relative potency of different opioids when initiating opioid therapy, changing from one route of administration to another and when changing from one opioid to another.

a. When changing from one opioid to another, clinicians are advised 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 possible incomplete cross-tolerance.
b. Most of the errors associated with preventable adverse drug events in hospitals occur at the ordering stage in treatment.[105]
c. Clinicians can be unaware of the potency of different types of opioids relative to each other or to morphine (i.e., morphine equivalent dose), which can lead to inadvertent overdose when initiating therapy with non-morphine opioids and when converting from one opioid to another.
d. Clinicians are advised to use extreme caution when performing conversions to and from methadone and consider consultation with a pharmacist, or pain management specialist when available, to assist with conversion decisions and calculations. Pharmacists may also be helpful in guiding decisions and calculations when converting to and from methadone or atypical opioid agents (i.e., buprenorphine, tapentadol).

12. Obstetrician-gynecologists are encouraged to prescribe naloxone to patients at elevated risk for opioid overdose.

a. In 2018, the U.S. Office of the Surgeon General issued an advisory urging health care systems to increase access to naloxone, joining the CDC, the World Health Organization (WHO) and the American Medical Association (AMA) in advocating for the wider availability of naloxone. The advisory states:
   i. "For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have OUD and community members who come into contact with people at risk for opioid overdose, knowing how to use naloxone and keeping it within reach can save a life."[106]

b. Although the CDC recommends that naloxone be prescribed for any patient who is discharged with an opioid prescription for more than 50 mg MME per day, clinicians are advised to view a patient's MME dosage as only one contributor to overdose risk. While risk of opioid overdose mortality does increase in a dose-dependent manner, there is no distinct risk threshold that permits identification of an MME dosage of an opioid that should automatically trigger or exclude a prescription for naloxone.[93] It is encouraged that all relevant patient factors, including medical, behavioral, social and environmental factors be considered. In addition, obstetrician-gynecologists are reminded that women experience overdose with exposure to lower opioid doses than men and that existing MME thresholds do not take this fact into consideration.[107]

c. It is advised that any patient on chronic opioid therapy (COT) be prescribed naloxone.

d. It is recommended that any patient discharged with a prescription for an opioid *and* any of the following conditions be prescribed naloxone:
   i. Known or suspected SUD (including alcohol use disorder [AUD])
   ii. Concurrent use of benzodiazepines or other sedatives
   iii. Rotated from one opioid to another because of increased tolerance or poor analgesic effects
   iv. History of tobacco use, chronic obstructive pulmonary disease (COPD), emphysema, asthma, sleep apnea, a respiratory infection or other pulmonary disease
   v. Renal dysfunction, hepatic disease, cardiac comorbidities or HIV/AIDS
   vi. Known or suspected uncontrolled depression or taking a prescription antidepressant
   vii. Unreliable access to emergency medical services

e. Obstetrician-gynecologists are encouraged to prescribe naloxone to any patient prescribed an opioid who has postpartum depression (PPD) or is assessed to be at risk for developing PPD. Women with SUD have high rates of comorbid mood disorders, which increase their risk for PPD.[108]

f. Clinicians can direct patients to BringNaloxoneHome.org for education on how to obtain and use naloxone.

Prescribing Naloxone Protects All Members of a Household[108]

- **Naloxone protects a patient's children and family:** A national survey of emergency department (ED) visits for treatment of opioid overdose found that on average 18 patients under the age of 18 are treated for opioid overdose every day in the United States, with children aged 2-3 and adolescents aged 17-18 most likely to be treated for overdose. Twenty-four percent of ED visits for opioid overdose in children were associated with intentional self-harm. Patients may be advised that naloxone should be present in households with children where opioids are present. While the need for safe storage is clear, having naloxone on hand provides an additional level of protection.

- **Naloxone protects a patient's pets:** Rates of opioid poisoning and overdose death in dogs have increased in parallel with that of humans. A study of canine opioid overdose finds a significant association between accidental opioid dog poisoning calls and county level human opioid prescription rates. Naloxone is effective in dogs, and patients may be advised that having naloxone available can safely reverse overdose in their pets.[109]

13. **It is recommended that gynecologic patients with chronic pain be treated in accordance with existing guidelines for management of chronic pain and/or co-management or referral to a pain specialist where available and appropriate.**
    a. In all cases, diagnosis and treatment of underlying disease is strongly recommended. When treatment is ineffective, obstetrician-gynecologists are encouraged to refer patients with refractory pain to chronic pain specialists rather than prescribed opioids.
    b. It is advised that obstetrician-gynecologists who manage COT for their patients with chronic gynecologic pain adhere to best practices in management of chronic pain as described in the following guidelines:
        i. *CDC Guideline for Prescribing Opioids for Chronic Pain*
        ii. *Interagency Guideline on Prescribing Opioids for Pain, Washington State Agency Medical Directors' Group*
        iii. *Pain Management Resources and Opioid Use, Colorado Department Of Health Care Policy and Financing*
        iv. *Pain Management Best Practices, U.S. Department of Health and Human Services*

Practice Recommendations for Hospitalized Patients

1. **Obstetrician-gynecologists are encouraged to use the oral route of administration for opioids whenever possible. Intravenous (IV) opioids are best reserved for patients who cannot take medications by mouth, patients with suspected GI malabsorption, and patients for whom immediate pain control or rapid dose titration is necessary.**
    a. IV administration is associated with an increased risk of side effects, adverse events and medication errors.[110-112]
    b. In general, rapid-onset medications have greater addiction potential. (Onset with IV administration is 5-10 minutes on average compared to 15-30 minutes with oral administration.)[113]
    c. Furthermore, the duration of action is greater with oral administration than with IV administration of opioids, which may allow for more consistent pain relief and less frequent administration.

2. **Obstetrician-gynecologist teams are encouraged to supplement numerical rating scales of pain intensity with functional assessments of pain. It is advised that the dosage and type of opioid prescribed not hinge solely on a patient's numerical estimation of pain intensity.[114]**
    a. In addition to subjective reports of pain intensity, it is suggested that safe, effective opioid dosing be based on a careful assessment of multiple objective measures, including the patient's age, comorbidities, sedation level, respiratory status, concurrent sedating medications and previous response to opioids.
    b. It is recommended that the practice of prescribing specific doses of opioids based solely on responses to a numerical pain intensity scale be avoided.
        i. Use of numerical rating scales has not been shown to improve pain control or patient outcomes.[115-119]
        ii. Patient reports of pain intensity are subjective and may be unreliable.[118]
        iii. The incidence of over-sedation with opioids more than doubled following the use of an acute pain treatment algorithm guided by a numerical pain rating scale.[120]
        iv. Administering opioid analgesics based solely on the intensity of a patient's discomfort can result in both the overtreatment and undertreatment of pain.[119,121]

c. There is no correlation between a given pain intensity score and an effective opioid dose.[122]
d. Ideally, pain assessment is conducted frequently and takes into consideration the patient's ability to sleep, ambulate, resume the activities of daily life and/or participate in physical therapy.[114,123,124]
   i. Patients prefer assessments that consider the impact of pain on function.[114,123,124]
   ii. While adoption of pain assessments that evaluate function may require additional involvement and education of nursing staff, nurses reported preferring the functional pain scales to one-dimensional pain intensity rating systems.[114] **SEE APPENDIX I, THE CLINICALLY ALIGNED PAIN ASSESSMENT** (CAPA), for an example of a pain assessment tool that incorporates functional changes.
e. During postsurgical visits, obstetrician-gynecologists are advised to inquire about pain control, emphasizing the importance of improvements in function and quality of life over numerical measurements of pain intensity.
   i. It is suggested that assessments of postsurgical pain on follow-up clinic visits emphasize functional parameters.
   ii. A prescription renewal request for an opioid is associated with a nearly doubled risk of developing OUD, and it is advised that such a request prompt an in-person discussion with the patient regarding the dangers surrounding opioid misuse.[125]
   iii. Consider early consultation with and/or referral to pain and/or behavioral health clinicians for patients with postoperative pain not typical for their procedure and in the absence of surgical complications. When managing patients without the aid of local pain medicine specialists, consider establishing consultant relationships with pain specialists at referral hospitals or telehealth centers.[126,127]

3. It is recommended that obstetrician-gynecologists order a bowel regimen to prevent opioid-induced constipation in patients receiving opioids unless contraindicated.

a. Constipation is a very common adverse effect of opioid therapy due to the activation of μ-opioid receptors in the colon, which results in decreased peristalsis. The limited mobility of hospitalized patients increases their risk of constipation, and the use of opioids during their hospitalization amplifies this risk.
b. Opioid-related constipation can cause an exacerbation of perineal pain in postpartum patients.
c. It is suggested that the administration of a bowel regimen be provided to all hospitalized medical patients receiving opioid therapy unless the patient is having diarrhea.
d. Given the mechanism of opioid-induced constipation, stimulant laxatives (e.g., senna, bisacodyl) are recommended as part of the bowel regimen with opioid therapy.[128] Newer agents for opioid-induced constipation including naloxegol, methylnaltrexone, alvimopan, lubiprostone and naldemedine are efficacious but significantly more expensive and may be considered for use when conventional therapies have failed.[129] Subcutaneous methylnaltrexone was shown to be more efficacious than lubiprostone, naloxegol and oral methylnaltrexone for opioid-induced constipation.[129]
e. Osmotic laxatives (e.g., polyethylene glycol, lactulose) have demonstrated efficacy for the treatment of constipation more generally, but not necessarily opioid-induced constipation. Due to the limited and conflicting evidence for efficacy in prevention or treatment of constipation, stool softeners are not recommended as monotherapy for opioid-induced constipation.[129]
f. Ideally, bowel movements are tracked during hospitalization and the bowel regimen modified accordingly.

Practice Recommendations for Surgical Patients

Preoperative Practice Recommendations

1. **Obstetrician-gynecologists are encouraged to counsel patients on the prehabilitative measures they may take to reduce postoperative pain and accelerate recovery.[130-134] The concept of surgical prehabilitation is relatively new and research is needed to determine precisely what medical, nutritional, physical conditioning and/or behavioral health optimization prior to surgery are most beneficial to patients.[135]**
   a. It is recommended that all patients be encouraged to stop smoking. Surgical patients may be additionally advised that smoking cessation may not only improve perioperative outcomes, but also that smoking may be associated with greater postoperative pain and opioid requirements.[132,136-138] The mechanism of the association between smoking and postoperative pain is not fully understood.[139]
      i. Nicotine and carbon monoxide are responsible for the immediate perioperative risks of smoking, which include cardiopulmonary complications, wound infection, impaired wound healing and bone fusion and prolonged hospitalization.[139,140] Patients may be educated that even 24-48 hours of smoking cessation may reduce risk.[139]
      ii. Consider prescribing patients nicotine replacement therapy (NRT) to aid in smoking cessation prior to elective surgery. A Cochrane review found evidence that preoperative NRT and behavioral support did increase short-term smoking cessation and may reduce postoperative morbidity.[141]
      iii. Evidence does not support postoperative benefits of nicotine replacement for surgical patients in pain management, though NRT may increase patient comfort after surgery.[133]
   b. Heavy alcohol use (at least five drinks [> 60 g ethanol] a day) is associated with poor surgical outcomes and increased postoperative pain and opioid requirements, possibly via changes to N-methyl-D-aspartate (NMDA) and μ-opioid receptor densities in chronic alcohol users.[142-147]
      i. A study in colorectal patients who were heavy alcohol users (without cirrhosis or clinical evidence of alcohol use) found better outcomes in patients treated with disulfiram for one month prior to surgery.[148] A Cochrane review of preoperative alcohol cessation prior to elective surgery also notes lower rates of surgical complications.[149]
         1. Consider referring patients who are heavy alcohol users to addiction medicine and/or behavioral health care for behavioral and pharmacologic strategies for relapse prophylaxis and management of alcohol withdrawal symptoms prior to elective procedures.[149]

2. **Obstetrician-gynecologists are encouraged to avoid prescribing opioids to opioid-naive patients prior to elective surgery.**
   a. It is suggested that opioid-naive patients awaiting surgery who are in pain be managed with opioid-sparing multimodal analgesia whenever possible.
   b. Patients who use opioids in the 30-day preoperative period are twice as likely to have persistent postsurgical opioid use.[17,33]
   c. It is recommended that opioid-naive surgical patients who have received a prescription for an opioid from another clinician in the immediate preoperative period be encouraged to cease or minimize their opioid use and be educated on the risks and benefits of opioids and nonopioid analgesics.
   d. Between 7-21% of patients receive at least one opioid prescription for acute pain during pregnancy.[150,151] When possible, it is advised that pregnant patients with acute pain be treated with nonpharmacologic and nonopioid interventions.

3. **Obstetrician-gynecologists are encouraged to develop a perioperative pain management plan with the patient's primary opioid prescriber when caring for patients receiving COT for pain.**
   a. As many as one in four patients report taking opioids prior to elective surgery.[152]
   b. Patients taking opioids prior to surgery have worse health outcomes, including longer hospital stays, increased costs, a greater need for discharge to rehabilitation facilities and more readmissions than opioid-naive patients.[153,154] COT predisposes patients to OIH, which may significantly complicate pain control after surgery.[155]
   c. It is suggested that obstetrician-gynecologists avoid escalating the preoperative dose of opioids when managing patients on COT.
   d. While it is advised that patients on COT not be routinely weaned off opioids prior to surgery, some patients may benefit from a reduction in opioid dose prior to an elective procedure. Decisions regarding opioid dosing should be patient-centered and made in consultation with the patient and all clinicians involved in the patient's care.
      i. In the rare case in which a patient must be taken off opioids, it is recommended that the strategy for weaning be individualized to the needs of the patient. It is advised that tapers be gradual enough to minimize withdrawal symptoms.[156]
      ii. Slower tapers (10% per month or slower) are better tolerated, especially by patients who have used opioids for more than one year.[157-160]
      iii. Faster tapers may be appropriate for patients who have used opioids for only weeks to months. A 10% decrease in the original dose per week or slower (until 30% of the original dose is reached) followed by a weekly decrease of 10% in the remaining dose is less likely to trigger withdrawal.[157,159]
      iv. Ultra-rapid detoxification under anesthesia is dangerous and should never be trialed.
      v. For guidance in safe tapering of chronic opioid therapy, see the HHS *Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics*.[156]
   e. Obstetrician-gynecologist teams are encouraged to involve pain specialists as appropriate in the care of surgical patients receiving COT.

4. **Use of a validated screening tool is advised to evaluate the patient's risk of developing OUD prior to any surgical procedure.[161] Consider obtaining a behavioral health evaluation, a consultation with a pain specialist and/or arranging additional psychosocial support throughout the perioperative period for high-risk patients.**
   a. No validated screening tools exist for the identification of patients at no or low risk for developing OUD. It is important to consider the potential vulnerability of every patient.[162]
   b. Multiple agencies, including the CDC and Colorado Department of Regulatory Agencies, advocate using an opioid risk screening instrument, such as the Opioid Risk Tool-Revised (ORT-R), the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) or the validated shortened version, SOAPP-8, to evaluate for factors that might predispose patients to opioid misuse and addiction.[163,164] While these tools have only been validated for patients with chronic pain, they may help identify patients who are at elevated risk for opioid misuse and addiction.[165]
   c. Those with a history of SUD, pain disorders and/or non-SUD behavioral health disorders appear to have the highest relative risk for developing OUD. Notably, only the absence of a mood disorder is associated with a reduced risk of developing OUD.[166]
   d. High-risk criteria for persistent opioid use after surgery include:[167,168]
      i. Personal or family history of any SUD (e.g., alcohol, illicit drugs, prescription drugs)[168-170]
      ii. Current tobacco use[32,167]
      iii. Preoperative opioid, benzodiazepine or antidepressant therapy[170]
      iv. History of a behavioral health disorder, including mood and anxiety disorders, personality disorders, somatoform disorders and psychotic disorders[17,166]
      v. Low income[171]
   e. No patients should be denied adequate perioperative analgesia due to concerns about their potential for addiction. Opioids may be cautiously administered even to patients determined to be at increased risk for OUD.

5. **Obstetrician-gynecologists are encouraged to assess for factors that may increase the risk of ORADEs prior to prescribing an opioid.[161]**
   a. Opioid-induced respiratory depression (OIRD) and opioid-induced unintended advancing sedation (OIUAS) have been estimated to occur in up to 4.2% of hospitalized patients who receive systemic or neuraxial opioids and may cause hypoxic or anoxic brain injury and/or death.[172]
   b. High-risk medical comorbidities include:
      i. Pulmonary comorbidities (e.g., COPD, obstructive or central sleep apnea)
      ii. Cardiac comorbidities (e.g., congestive heart failure)
      iii. Organ dysfunction (e.g., renal or hepatic failure)
      iv. Obesity (BMI ≥ 30 kg/m2) and obesity hypoventilation syndrome
   c. Other patient factors include:
      i. Age greater than 65 years
      ii. Current or past smoker and/or preoperative need for supplemental oxygen
      iii. History of difficult-to-control postoperative pain or over-sedation with opioids
      iv. Presurgical opioid use, opioid tolerance or high MME requirement
      v. Current or prior SUD (including AUD)[147,148]
   d. Procedure- and treatment-related factors include:
      i. Use of general anesthesia, especially longer than six hours
      ii. Operation on the upper abdomen
      iii. Use of continuous opioid infusion
      iv. Concurrent use of other sedating agents[173,174]
      v. History of or current OIUAS or OIRD (i.e., in the post-anesthesia care unit [PACU])
      vi. History of previous use of naloxone

6. **Obstetrician-gynecologists are encouraged to assess patients for the risk of difficult-to-control postsurgical pain and consider the early involvement of pain and behavioral health services as appropriate. Behavioral health conditions, acute preoperative anxiety, catastrophizing, a history of chronic pain, severe preoperative pain and/or preoperative opioid use may increase the likelihood of difficult-to-control postoperative pain.[138,175-177]**
   a. Patients on COT are at increased risk of heightened postoperative pain.[84] Patients with a prior diagnosis of chronic pain or significant preoperative pain may benefit from the close involvement of pain and behavioral health services.[136]
   b. Preoperative anxiety may be a predictor of heightened postoperative pain and increased opioid consumption.[136,178-180] It is recommended that the management of acute preoperative anxiety be tailored to the patient. Consider using gabapentinoids, clonidine or melatonin for patients with acute perioperative anxiety. (See discussion of anxiolytics in **SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE**, "Nonopioid Pharmacologic Agents for Multimodal Analgesia.")

7. **It is recommended that prior to surgery, patients be assessed for the risk of developing chronic postsurgical pain (CPSP), a common surgical complication that may increase the long-term risk of opioid misuse, dependence and addiction.[125,181]**
   a. While rates of CPSP vary widely depending on the procedure studied and the definitions used, a study of patients undergoing a range of gynecologic surgeries found that 14% reported pain six months following surgery.[182] Rates were higher (23%) among patients with preoperative pelvic pain and in patients reporting pain in another body part (17%). Abdominal procedures are consistently more likely to produce CPSP than vaginal procedures. Rates of CPSP after vaginal and laparoscopic hysterectomy in other reports range from 5-50%.[183,184] Approximately 40% of patients are reported to have persistent pain three months following cesarean delivery, and 10-20% of parturients have persistent post-cesarean pain up to a year following delivery that is severe enough to interfere with their quality of life on a near-daily basis.[185]

b. Severe immediate postoperative pain has been identified as a risk factor for CPSP. Other potential risk factors for CPSP include:
   i. Duration of surgery[186]
   ii. Female sex
   iii. Genetic factors
   iv. Obesity
   v. Preexisting pain in any location
   vi. Psychological factors (anxiety or depression)
   vii. Tobacco use
   viii. Younger age
c. While no validated screening protocol exists, Appendix II, Risk Index for the Prediction of Chronic Postsurgical Pain, includes a screening tool that can help identify those at elevated risk of developing CPSP with a reported sensitivity of 60% and a specificity of 83%.[187]
d. Preventive strategies are encouraged for patients at high risk of developing CPSP, including modified surgical techniques, multimodal pain control throughout the perioperative period and interventions focused on psychosocial and cognitive behavioral risk factors.[188] Use of regional anesthesia may reduce the risk of CPSP after some procedures.[189-191]
e. Limited evidence suggests that use of amine reuptake inhibitors, gabapentinoids, topical lidocaine and/or capsaicin, ketamine, clonidine and/or intraoperative use of lidocaine infusion may reduce the incidence of CPSP.[188] **(SEE SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE.)**
f. For patients at high risk of CPSP, the early involvement of pain services is optimal.
g. Obstetrician-gynecologists are encouraged to consider the likelihood a patient will experience CPSP while thoroughly explaining the risks and benefits of elective procedures, including cosmetic surgery. In some cases, it may be prudent to delay surgery until these risk factors have been addressed.

Practice Recommendations for Discharge Prescribing

1. **Obstetrician-gynecologists are encouraged to prescribe the minimum quantity of opioids anticipated to be necessary upon discharge using a shared decision-making model with the patient. Obstetrician-gynecologist practices are advised to establish standard prescribing practices and default limits. Table 6 provides procedure-specific guidance for opioid prescription following common surgeries.**
   a. Opioid-naive patients who received opioid prescriptions upon hospital discharge are at increased risk for chronic opioid use.[192] Receiving higher intensity and/or longer duration opioid therapy in the setting of acute pain has been associated with an increased risk of long-term disability and long-term opioid use.[193-195]
   b. For those with ongoing pain that is severe enough to require opioids after hospital discharge, it is recommended that decisions regarding the duration of therapy be made on a case-by-case basis, ideally using a shared decision-making model.[34,196,197] Generally provision of a one- to three-day supply will be sufficient.
   c. Pain management plans that are individualized to the patient may reduce opioid exposure. It is recommended that discharge opioid prescribing take into account each patient's:
      i. Standardized prescribing recommendations, if available
      ii. Inpatient opioid requirements
      iii. Level of pain and function prior to discharge
      iv. Medical comorbidities
      v. Risk factors for OUD and ORADEs
      vi. Patient preferences surrounding opioid analgesia
   d. It is suggested that patients who required no opioids in the 24 hours prior to discharge not be routinely discharged with a prescription for an opioid.[30]
   e. If breakthrough pain is a concern, surgeons may consider writing a prescription for a small quantity of opioids (i.e., a quantity sufficient to provide coverage for one or two days until the patient can be evaluated in clinic), with instructions to fill it only if necessary.

(TABLE 6)

Suggested Ranges for Discharge Quantity of Opioid Tablets Following Common Obstetric and Gynecologic Surgical Procedures Based on Research and Expert Opinion

Note: Numbers represent 5 mg tablets of oxycodone or equivalent. Opioid monoproducts are favored over combination formulations (e.g., with acetaminophen), as it is recommended that patients be encouraged to take acetaminophen independently prior to resorting to an opioid.

	Johns Hopkins University	Mass General/ Brigham & Women's Hospital	Michigan OPEN	CO's CURE
Laparoscopic or vaginal hysterectomy	0-10		0-15	0-15
Abdominal hysterectomy	0-20		0-20	0-20
Uncomplicated cesarean delivery	0-10	0-20	0-20	0-20
Uncomplicated vaginal delivery	0	0		0
Diagnostic laparoscopy				0-10
Postpartum tubal ligation				0-10
Hysteroscopy/dilation and curettage (D&C)				0

SOURCES: Overton HN, Hanna MN, Bruhn WE, et al. Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus.[198]
Hill MV, Stucke RS, Billmeier SE, Kelly JL, Barth RJ. Guideline for Discharge Opioid Prescriptions after Inpatient General Surgical Procedures.[199]
Opioid Prescribing Engagement Network (Michigan OPEN). Prescribing Recommendations.[200]

2. **Obstetrician-gynecologist clinician groups are urged to collect, track and share individual opioid ordering and prescribing patterns among their fellow clinicians to decrease variability in opioid prescribing at discharge.**
   a. Obstetrician-gynecologists comprised 0.9% of the total high-volume opioid prescribers from 2016-2017.[201] High-volume prescribing was defined as the top 10% of opioid prescribers based on the total number of opioid prescriptions in a 12-month period. The prescribing patterns of opioid medications vary substantially among obstetrician-gynecologists.[202,203]
   b. A knowledge of current ordering patterns is critical for protocol implementation, clinician education and quality improvement measures.[201] Tracking in-hospital opioid ordering patterns and providing comparative data to those within a practice may help reduce discrepancies and identify clinicians who can benefit from further education in multimodal analgesia.
   c. It is suggested that this information not be used punitively, but rather to help clinicians understand their own treatment habits and facilitate change.

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 hospital workflows.
   b. Although there is no national data-sharing protocol that crosses state lines, a number of states participate in data-sharing hubs. Without data from surrounding localities, PDMPs cannot provide clinicians with full prescribing information. Access to nationwide data on opioid prescribing practices would enable clinicians to better detect aberrant patterns of opioid prescribing and encourage their patients to seek treatment. Legislation is needed to establish a national PDMP and foster the broad exchange of prescribing information.
   c. Providers are required to use two separate logins to access their EHRs and PDMPs, a drawback that can make the use of PDMPs cumbersome and disruptive. Legislation that encourages the direct and automatic integration of PDMP data within EHRs would enable the seamless reconciliation of a patient's opioid prescription history with their current medications and health care needs.
   d. Automatic queries linked to hospital registration significantly increase the use of PDMPs in clinical decision-making.[204] Systems that incorporate such technology are overwhelmingly favored by clinicians, 98-100% of whom report improved access.[205]

2. **Pain should not be considered the "fifth vital sign," and clinical medicine should move to deemphasize numerical rating scales and incorporate functional assessments into pain management pathways.**
   a. Long promoted as the "fifth vital sign," pain has developed enormous leverage in the American medical lexicon. Medicine has overemphasized pain; as a result, physicians often feel pressured to prescribe opioids to normalize this "vital sign." In response, the AMA has issued a statement that pain should not be considered the fifth vital sign.[206]
   b. While a patient's discomfort is an important element of any clinical evaluation, clinicians are advised to consider it simply as one component of a global clinical assessment, along with objective measurements such as heart rate, respiratory rate and blood pressure. Pain is a complex biopsychosocial phenomenon that cannot be distilled into a one-dimensional numerical "target."
   c. Numerical pain scores have been shown to increase the risk of overtreatment and unintentional overdose in hospital settings.[121] Functional pain scales, which focus on a patient's ability to perform daily activities, are more clinically relevant than numerical scores, and their use is less likely to result in the overtreatment of pain.[123,124]

3. **Private and public insurers should provide adequate compensation for the time and expertise required for the universal adoption of appropriate screening measures (e.g., extensive history taking, review of medical records, PDMP queries, urine toxicology screenings, etc.).[207]**
   a. Patients are often reluctant to disclose information about their substance use, particularly on written or quickly administered verbal questionnaires. Obtaining an accurate substance use history may require additional clinical skill and time.
   b. Patients with SUD may require referrals to primary care clinicians and addiction medicine, pain management and behavioral health specialists. Adequate reimbursement for coordinated care facilitates the comprehensive management of surgical patients with behavioral health needs.

4. **State and federal agencies should expand educational outreach to clinicians and the public in safe storage and disposal of excess opioid medication and should increase opportunities for safe drug disposal.[207]**
   a. Provide streamlined processes for clinician offices, pharmacies, hospitals and other public offices to become safe disposal sites.
   b. Support medication safe disposal drop box locations in each county so that safe disposal sites are easily accessible to Coloradans in both urban and rural areas.
   c. Maintain a database of statewide safe disposal locations to be made available to the public.
   d. Consider providing financial incentives for organizations that participate in safe disposal programs.
   e. Launch targeted statewide public health campaigns to educate the public on the importance of safe disposal and statewide locations of safe drug disposal sites.

Multimodal Analgesia in Obstetric and Gynecologic Practice

c|h|a Colorado Hospital Association

COLORADO MEDICAL SOCIETY

COLORADO CONSORTIUM for Prescription Drug Abuse Prevention

Multimodal Analgesia in Obstetric and Gynecologic Practice

The irony of the current epidemic of opioid overdose death and OUD is that the opioids liberally prescribed with the best of intentions over the past two decades have not effectively treated Americans' pain. Pain remains a leading cause of disability and a major contributor to health care costs in the United States today.[207] Women experience both chronic and acute pain at higher rates than men, likely as a result of genetic, gender, anatomic and physiologic differences. [208-210] Evidence suggests that compared to males, females have heightened sensitivity to most forms of induced pain.[208,211]

Despite the ubiquity of pain in clinical practice, pain is poorly understood by many medical professionals and seldom taught in medical schools, 96% of which have no dedicated pain medicine modules.[212] A better understanding of pain and the interventions that can be therapeutically applied to alleviate it is among the most important aspects of better opioid stewardship and safer analgesia. Appendix III, Understanding Pain: A Complex Biopsychosocial Phenomenon, provides a brief overview of how clinicians should conceptualize pain.

Most surgical patients experience some degree of pain after surgery. Despite the near-universal use of short courses of opioids perioperatively, as many as 80% of patients report moderate to extreme postoperative pain.[213,214] Surgical pain is multifactorial and, depending on the procedure, may involve nociceptive pain associated with incision and surgical injury, visceral pain associated with disruption of visceral structures, neuropathic pain secondary to nerve damage or transection, and the systemic inflammatory response to tissue damage. Compounding pain caused by surgery itself, many patients have a history of chronic pain or present with conditions that are acutely painful. Thus, perioperative pain is often complex and multifactorial.

Simply put, opioids are less effective for the treatment of many types of pain than nonopioid medications and interventions. Moreover, the immediate adverse effects of opioids, including respiratory depression, sedation, nausea and vomiting, urinary retention and ileus, make their use risky, particularly in surgical patients. Such ORADEs are common, with an estimated 10-13% of surgical patients experiencing an ORADE.[215,216] Patients with ORADEs are estimated to have a 55% longer length of stay, 47% higher cost of care, 36% increased risk of 30-day readmission and 3.4 times higher risk of inpatient mortality than those without.[216,217] Of further concern is mounting evidence that opioid use may itself predispose patients to development of OIH and chronic pain syndromes.[64,65] Finally, evidence suggests that opioids may 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.[62,63,218] Research is ongoing to further understand this association, but the possibility that opioids may worsen patient outcomes underscores the importance of judicious opioid prescribing.[62,63,218] In many cases, the medications meant to ease patients' suffering may in fact contribute to it.

Pain is best addressed by simultaneously intervening at multiple points in the physiologic pathways involved in the transmission of pain signals. By selecting pharmacologic agents that act on different channels, enzymes and receptors, obstetrician-gynecologists can leverage the additive and synergistic mechanisms of analgesia provided by complementary medications to treat pain more comprehensively. At the same time, obstetrician-gynecologists also have a powerful array of regional anesthetic and analgesic interventions at their disposal, which, if used widely and consistently, have the potential to provide anatomically selective anesthesia and analgesia, further reducing the need for systemic analgesics. Evidence supporting the concomitant use of regional and nonopioid pharmacologic analgesia for acute perioperative pain is strong, and the possibility that such multimodal approaches may reduce the incidence of CPSP may additionally motivate obstetrician-gynecologist surgical care teams to use multiple modes of pain control for all their patients.[186,188,191,219-222]

Multimodal Analgesia in Obstetric and Gynecologic Practice continued

An obvious, practical approach to reducing the national reliance on opioids is to offer every gynecologic or obstetric surgical patient nonopioid analgesics. Despite the limitations of opioids and ample evidence in support of alternatives to opioids, physicians and hospitals frequently fail to offer surgical patients more than one mode of pain control. While virtually every surgical patient in the United States receives opioid analgesia, the likelihood of receiving a single nonopioid analgesic after surgery ranges from 43-99% depending on the institution, while the likelihood of receiving two nonopioid agents ranges from 8-92%.[223]

Opioid monotherapy often fails to achieve adequate analgesia and exposes patients to both increased immediate risk of ORADEs and long-term risk of dependence and addiction. For many patients, scheduled acetaminophen and an NSAID, unless contraindicated, provides adequate analgesia. For others, the addition of one or more of the nonopioid therapies may reduce or eliminate perioperative opioid requirements while simultaneously improving pain control and the speed of recovery.[224-226] Obstetrician-gynecologists 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, obstetrician-gynecologists must contend with the lack of high-quality, procedure-specific evidence for many of the suggestions outlined in the pathways below.[227] Further research is urgently needed to determine the quality of evidence and strength of recommendations for many elements in these pathways. 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 clinicians partner with researchers, pharmacists 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

Note: Not all of the following recommendations apply to the management of pain in pregnancy. Special considerations for pharmacological therapy in pregnancy and lactation are required.

1. **Obstetrician-gynecologists are encouraged to use multimodal analgesia and adopt the following principles when managing pain:**
   a. Use nonopioid approaches as first-line therapies.
   b. Use several pharmacological agents and/or regional anesthetic/analgesic interventions for pain control rather than relying on opioid monotherapy.
   c. Use opioids primarily as rescue medications.
   d. Emphasize realistic, functional pain management goals with patients.
   e. Use empathic language when discussing pain.
2. **Obstetrician-gynecologists are encouraged to adopt enhanced recovery pathways (ERPs) and support the institutional adoption of enhanced recovery protocols in hospitals where they perform surgeries.**
   a. For full ERAS guidelines for many common obstetric and gynecologic procedures see:
      i. ACOG Committee Opinion 750: Perioperative Pathways Enhanced Recovery After Surgery
      ii. Guidelines for postoperative care in cesarean delivery: Enhanced Recovery After Surgery (ERAS) Society recommendations
      iii. SOAP Enhanced Recovery After Cesarean (ERAC) Full Consensus Statement
      iv. ERAS Society/ERAS USA
      v. Guidelines for Perioperative Care in Gynecological Oncology, 2019 Update

(TABLE 7)

ACOG Committee Opinion Number 750[228]

The American College of Obstetricians and Gynecologists makes the following recommendations and conclusions regarding the implementation of Enhanced Recovery After Surgery (ERAS) pathways:

- Enhanced Recovery After Surgery pathways were developed with the goal of maintaining normal physiology in the perioperative period, thus optimizing patient outcomes without increasing postoperative complications or readmissions.[229]
- The goals of decreasing surgical stress and helping the body mitigate the consequences of such stress with ERAS pathways is achieved by the implementation of a combination of multiple elements, which when bundled together, form a comprehensive perioperative management program.
- The basic principles of ERAS include attention to the following: preoperative counseling and nutritional strategies, including avoidance of prolonged perioperative fasting; perioperative considerations, including a focus on regional anesthetic and nonopioid analgesic approaches, fluid balance and maintenance of normothermia; and promotion of postoperative recovery strategies, including early mobilization and appropriate thromboprophylaxis.
- Benefits of ERAS pathways include shorter length of stay, decreased postoperative pain and need for analgesia, more rapid return of bowel function, decreased complication and readmission rates, and increased patient satisfaction.[229-236] Implementation of ERAS protocols has not been shown to increase readmission, mortality or reoperation rates.
- Institutions considering adoption of ERAS programs should carefully examine their own infrastructure and patient flow through the preoperative and postoperative phases of care.
- In order for an ERAS program to be sustainable, it should be embedded as a standard model of care in a health care delivery system.
- Enhanced Recovery After Surgery is a comprehensive program, and data demonstrate success when multiple components of the ERAS pathway are implemented together.
- The use of ERAS pathways should be strongly encouraged within institutions.

NOTE: "ERAS" is a term trademarked by the ERAS Society USA. For the purposes of these guidelines "enhanced recovery protocol (ERP)" is interchangeable with "ERAS."

Multimodal Analgesia in Obstetric and Gynecologic Practice continued

3. **Obstetrician-gynecologists are encouraged to employ surgical techniques that minimize tissue damage and inflammation.**
   a. Minimally invasive techniques result in less postoperative pain and lower opioid requirements.
      i. For laparoscopic procedures, obstetrician-gynecologists are encouraged to limit residual CO2 gas and intraoperative intra-abdominal pressures. Consider the following:
         1. Reducing the intra-abdominal pressure limit to 10 mm Hg (from 15 mm Hg) after dissection is complete.
         2. Removing as much intra-abdominal gas as possible, by placing the patient in the Trendelenburg position and having the anesthesiologist induce a Valsalva maneuver. This action has been shown to significantly improve pain control compared to placebo intervention.[237]
         3. Use of humidified CO2, which has been demonstrated to reduce pain in laparoscopic surgery.[238,239]
      ii. Injection of port sites extending to the subcutaneous, fascial and peritoneal layers with a long-acting local anesthetic is advised.
   b. Careful patient positioning reduces the likelihood of extremity or back pain or injury.
   c. Obstetrician-gynecologists are encouraged to preserve nerves and minimize disruption of tissue whenever possible.
   d. A trial of appropriate conservative measures is recommended prior to considering surgical interventions for the treatment of pain. If surgery is warranted, care must be taken to ensure that the procedure has a high likelihood of success and is well supported in the literature.

4. **Consider neuraxial and regional anesthetic techniques that may be applicable to each case and the risks and benefits of each.**
   a. Surgical teams are encouraged to work together to select the modes of neuraxial anesthesia, peripheral nerve or plane blocks, single-shot blocks and/or catheter placement for continuous wound infiltration (CWI) that are safe, effective and best suited to each patient and procedure in order to reduce postoperative pain and opioid requirements.
   b. Surgical teams may consider wound infiltration with amide anesthetics and/or, in appropriate patients, CWI or instillation of intraperitoneal local anesthetic (IPLA).
      i. Wound infiltration and/or port site infiltration with amide anesthetics has been demonstrated to reduce pain and analgesic requirements.[240-242]
      ii. Infiltration of the mesosalpinx and stump tissue with amide anesthetics at the time of postpartum tubal ligation has been demonstrated to reduce opioid requirements.[243]
      iii. Across a range of abdominal procedures, including cesarean delivery, IPLA has been shown to treat intraoperative pain, decrease early postoperative pain and opioid requirements and shorten length of hospital stay.[244-252]
   c. Collaboration between obstetrician-gynecologists and anesthesiologists may require the restructuring of operative workflows to efficiently facilitate the wider use of regional anesthetic interventions.
   d. Ideally, a regional anesthesia/analgesia plan will be in place prior to surgery in the event that a laparoscopic procedure must be converted to an open procedure.
   e. Patients should be informed of the risks and benefits of regional anesthesia/analgesia and patient informed consent be obtained prior to surgery for the use of any appropriate regional anesthesia/analgesia in the case that such an approach becomes indicated if not initially planned.
      i. It is recommended that standard preoperative consent forms be amended to facilitate the use of any appropriate regional anesthetic and analgesic interventions.
   f. Obstetric-gynecologic and anesthesiology teams can work with hospitals to ensure that they are credentialed and have the equipment necessary to perform opioid-sparing regional procedures.

5. Consider the use of opioid-sparing or opioid-free anesthesia protocols when clinically appropriate.

a. Opioid-sparing or opioid-free anesthesia (OFA) may be feasible and effective for a range of surgical procedures.[172, 253] OFA has demonstrated significant improvement in quality of recovery after ambulatory and laparoscopic gynecologic procedures compared to procedures in which anesthetic protocols included an opioid.[254,255]
   i. Minimizing the patient's exposure to opioids reduces respiratory depression, ileus, nausea, vomiting and sedation in the immediate postoperative period.
   ii. Minimizing the patient's intraoperative opioid exposure spares the μ-receptors for early postoperative analgesia by preventing the occurrence of an acute tolerance phenomenon.[256]

b. Although the intraoperative use of opioids is associated with OIH in the immediate postoperative period, the long-term implications of intraoperative opioid exposure are unknown.[257-259]

c. While there are no large studies comparing outcomes of OFA and usual care, OFA has been shown to be safe and feasible in small studies and case reports of a range of general surgical procedures, where a smoother emergence and lower immediate postoperative pain have been reported.[254,255,260]

d. OFA may be particularly appropriate for patients with COPD, obstructive sleep apnea, obesity hypoventilation syndrome, prior OIRD, those with a history of OUD and patients who request OFA.

6. Use of nonopioid medications are encouraged in the preoperative, intraoperative and postoperative periods to reduced postoperative pain and analgesic requirements.

a. Strongly consider concomitantly prescribing scheduled acetaminophen and an NSAID for the treatment of perioperative pain.
   i. It is suggested that acetaminophen be used both pre- and postoperatively for any surgical patient in whom it is not contraindicated. For lengthy procedures (> 6 hours), consider use of IV acetaminophen to maintain schedule in patients under anesthesia unable to take medication PO or PR.
   ii. It is recommended that NSAIDs be strongly considered for pre- and postoperative pain management, unless contraindicated. Although NSAIDs have in the past been avoided out of surgical, renal and bleeding concerns, more recent research supports the perioperative safety of these medications for the majority of surgical procedures.
   iii. Unless clinically contraindicated, it is suggested that all surgical patients receive scheduled doses of acetaminophen and an NSAID postoperatively and other multimodal analgesic interventions as appropriate.[71,261,262]
   iv. Low-dose, sub-dissociative ketamine is an effective analgesic that can be opioid-sparing during and following many different surgeries, including hysterectomy. It may be particularly beneficial for patients with chronic pain or opioid dependence.[263]
   v. Alpha-agonists (dexmedetomidine,[264-271] clonidine[265,272-275]), NMDA antagonists in addition to ketamine[263,276] (magnesium,[277-285] dextromethorphan[286-288]) and esmolol are agents that may have analgesic benefit for some patients undergoing surgery.
   vi. IV lidocaine is an effective perioperative analgesic, including for use in hysterectomy; it is recommended that its routine intra- and postoperative administration be supported by appropriate education and hospital policies.
   vii. Consider using an amine-reuptake inhibitor (e.g., duloxetine) or a gabapentinoid when CPSP is anticipated or when managing patients with preexisting chronic pain conditions. Consider coordinating with primary care or pain clinicians who can manage the ongoing use of these agents.
   viii. Consider the use of topical medications for postoperative pain control, including topical lidocaine.
   ix. For descriptions of the many nonopioid analgesics available, see "Nonopioid Pharmacologic Agents for Multimodal Analgesia" in **SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE**.

7. **For patients whose pain is exacerbated by significant perioperative anxiety, it may be helpful to prescribe an anxiolytic agent in the perioperative period, such as:**
   a. Oral or sublingual melatonin
   b. Oral clonidine
   c. Oral gabapentin
   d. The routine use of benzodiazepines in the postoperative period is NOT recommended, and obstetrician-gynecologists are advised against discharging patients on concomitant benzodiazepines and opioids. For select patients, low and limited doses of benzodiazepines may be appropriate.
   e. See agent descriptions in "Nonopioid Pharmacologic Agents for Multimodal Analgesia" in **SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE.**

8. **Obstetrician-gynecologists are encouraged to integrate multimodal treatment strategies and pathways into their computerized physician order entry systems to facilitate the seamless adoption and safe delivery of novel medications.**

9. **If no contraindications exist, it is suggested that acetaminophen and an NSAID be prescribed as scheduled analgesics for most acutely painful gynecologic and obstetric conditions.**
   a. The combination of acetaminophen and ibuprofen has been shown to be more effective than any opioid for a range of nonoperative pain conditions and for pain associated with surgical and dental procedures.[289-291]
   b. It is recommended that multimodal analgesia be offered to every surgical patient who reports pain. Multimodal analgesia can reduce opioid requirements and provides more effective pain control than opioid monotherapy across a range of operative and nonoperative painful conditions.[224-226]
   c. Although the perioperative use of multimodal anesthesia is recommended by numerous medical societies, adoption of this practice varies widely among clinicians and institutions. While virtually every surgical patient in the United States receives opioid analgesia, the likelihood of receiving a single nonopioid analgesic after surgery varies widely by institution.[223]
   d. It is advised that opioids be used for breakthrough pain only.[292-294] It is recommended that opioids be ordered only as needed to avoid over-sedation and unnecessary administration. Electronic ordering systems should default to the lowest possible doses of opioid.
   e. It is recommended that opioids not be prescribed as a scheduled medication for acute pain and that opioid monotherapy for the control of postsurgical pain rarely, if ever, be used, as it provides suboptimal relief and increases the likelihood of complications.[295]

10. **Prioritize nonpharmacologic options that can be used concomitantly with nonopioid pharmacologic options and regional anesthesia for the treatment of all types of pain.**
    a. Although few studies have assessed the benefit of nonpharmacologic, non-procedure-based therapies for the treatment of gynecologic and obstetric surgical patients, such therapies carry little to no risk, may have potential benefit and can be safely adopted.
    b. Simple nonpharmacologic therapies that are available to patients in many hospital settings include music therapy, cold or hot packs, chaplain or social work visits, mindfulness training and physical therapy.[296]
    c. The use of cognitive and behavioral therapies may be considered for patients at elevated risk for opioid misuse or addiction, difficult-to-control postoperative pain and/or CPSP.

11. **Consider the use of opioid-sparing multimodal pain management pathways for the following surgical procedures:**
    a. Hysterectomy
    b. Cesarean delivery

12. **Consider the use of opioid-sparing multimodal pain management pathways for the following gynecologic conditions:**
    a. Chronic pelvic pain
    b. Vulvodynia
    c. Primary dysmenorrhea
    d. Ovarian cyst
    e. First-trimester miscarriage
    f. Perioperative pain in gynecologic patients receiving MAT

13. **Consider the use of opioid-sparing multimodal pain management pathways for the following nonsurgical obstetric conditions:**
    a. Management of pain during labor and delivery
    b. Management of pain after vaginal birth

14. **Obstetrician-gynecologists are encouraged to consult as needed with pain and/or addiction specialists to manage acute pain in patients who are opioid-dependent, including patients receiving chronic opioid therapy and those receiving treatment with opioid agonists for OUD.**

15. **Clinicians are advised to be aware of and educate patients about the challenges and complications associated with providing analgesia and anesthesia to patients who use cannabinoids. With the effective legalization of cannabis in Colorado, obstetric-gynecologic patients increasingly present who use cannabis chronically and/or who have used cannabis in the immediate preoperative period. (See Appendix IV, Cannabinoids and Pain, for a detailed examination of this topic.)**
    a. Both recent and chronic cannabis use may alter anesthetic and analgesic requirements and effectiveness.
    b. Patients may mistakenly believe that cannabinoids are effective analgesics.
    c. Clinicians and patients are also advised to be aware of the possibility of cannabis withdrawal syndrome in hospitalized patients.

Multimodal Pain Management for Obstetric and Gynecologic Surgeries

Regional Anesthesia

Neuraxial analgesia, anesthesia, peripheral nerve and plane blocks comprise the cornerstone of opioid-sparing multimodal pain management in much of obstetric-gynecologic practice. Use of these modalities as components of a full enhanced recovery protocol often provides optimal opioid-sparing anesthesia and analgesia. Neuraxial analgesia is the only option for complete pain relief as a labor analgesic and is utilized for majority of labor parturients in the United States. Consistent, appropriate use of both established and novel regional anesthetic techniques has the potential to improve gynecologic surgical and obstetric outcomes, reduce the need for opioid analgesia and avoid many of the risks associated with general anesthesia.

The advent of ultrasound guidance in the late 1970s paved the way for advances in the development of peripheral nerve and plane blocks.[601-603] Because peripheral nerve and plane blocks have fewer cardiovascular and pulmonary effects, their safety profiles are in some cases superior to those of spinal and epidural techniques. Wider use of blocks, including transversus abdominis plane blocks, quadratus lumborum blocks, erector spinae blocks and ilioinguinal/iliohypogastric blocks, may be particularly valuable in cases where neuraxial anesthesia or analgesia are not feasible or for patients who are opioid-dependent or who have complex pain presentations. Use of continuous wound infusion, too, has potential to provide excellent opioid-sparing postoperative analgesia in both gynecologic and obstetric settings.

It is essential that all members of the surgical team communicate to determine the optimal options and plan for each patient and procedure. Of course, no intervention is without potential for harm, and obstetrician-gynecologists and anesthesiologists are advised to make every effort to minimize the risks of nerve and vascular injury, bleeding, infection, intravascular injection, local anesthetic systemic toxicity (LAST), injury to surrounding anatomic structures and inadequate block. This is a rapidly evolving area of perioperative care, and obstetric and gynecologic surgical teams serve their patients best by staying abreast of research and developments in the field. While full descriptions of available peripheral nerve and plane blocks is outside the scope of these guidelines, further detail is provided in **APPENDIX V, RISKS, BENEFITS AND CONTRAINDICATIONS OF PERIPHERAL NERVE AND PLANE BLOCKS**; and **APPENDIX VI, PERIPHERAL NERVE AND PLANE BLOCKS FOR COMMON OBSTETRIC AND GYNECOLOGIC SURGICAL PROCEDURES**.

Multimodal Analgesic Pathways for Obstetric and Gynecologic Surgeries

The following recommendations are derived from existing ERPs, a comprehensive literature review and expert opinion and have been reviewed by the CO's CURE editors. The clinical judgment of obstetrician-gynecologists and anesthesiologists must always supersede suggested clinical care pathways.

These multimodal analgesic pathways for hysterectomy and cesarean delivery offer interventions that may be useful for improving perioperative pain management and limiting patient opioid exposure. Many of the suggested multimodal analgesic modalities described in these sample pathways are applicable to other gynecologic surgeries. Obstetric-gynecologic surgical teams are encouraged to select from these options the pharmacological and regional anesthetic interventions that are best suited to each patient and procedure. It is in no way intended that most or all of the interventions listed below be used for any one patient or procedure. For **every** patient, the risks and benefits of **every** intervention and combination of interventions must be carefully weighed in consultation with the patient and the entire surgical team. It is recommended that multimodal analgesic interventions be carefully selected in order to address pain at multiple anatomic and physiological junctures.

These pathways are limited to considerations of pain and analgesia. Many of the recommendations for nonopioid anesthesia and analgesia presented are derived from existing ERPs. Surgeries conducted using comprehensive enhanced recovery protocols have been demonstrated to result in reduced postoperative pain and analgesic requirements, and obstetrician-gynecologists and anesthesiologists may consider developing and implementing full ERPs at their institutions where feasible and clinically appropriate.

It is recommended that multimodal analgesic regimens be tailored to safely meet the needs of individual patients and that medication selection and dosages be adjusted based on patient-specific factors, including organ function, comorbidities, home medication regimens and previous medication intolerances. Several of these drugs and blocks when administered together or in combination with anesthetic drugs or opioids can contribute to perioperative bradycardia, dysrhythmias, hypotension, local anesthetic systemic toxicity, renal disease, respiratory depression, somnolence and other adverse effects. The risk of these adverse effects can be decreased by eliminating certain 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. It is critical to understand the administration instructions, benefits and risks of each block, drug and block/drug combination. Anesthesiologists and obstetrician-gynecologists are encouraged to consult a pharmacist for guidance regarding the use of the agents in these pathways as needed. Evidence supporting the medication recommendations presented here is available in "Nonopioid Pharmacologic Agents for Multimodal Analgesia," in this section. For further detail on agents used in regional anesthesia, see **APPENDIX VII, PRIMARY AND ADJUNCTIVE PHARMACOLOGIC AGENTS FOR REGIONAL ANESTHESIA**.

Opioid-Sparing Multimodal Analgesic Pathway for Hysterectomy

Preoperative Recommendations	Consider for Preoperative Use
• Acetaminophen 1000 mg PO once	• COX-2 NSAID (celecoxib 200-400 mg PO once ***OR*** meloxicam 7.5-15 mg PO once) • Magnesium sulfate 50 mg/kg slow IV bolus • For patients with SUD or history of difficult-to-manage postoperative pain consider: - Gabapentin 300-600 mg PO once ***OR*** pregabalin 75-150 mg PO once (adjust the dose for age, renal function)[297,298] - Consider duloxetine 60 mg PO once • Dextromethorphan 90 mg PO once[286,299,300] • For patients with marked anxiety consider: - Melatonin 6 mg PO once[301-304] - Clonidine 0.1 mg PO once[265,305,306]

NOTE: It is recommended that preoperative oral agents listed be administered 30-90 minutes prior to procedure.

Intraoperative Recommendations	Consider for Intraoperative Use
Operative technique: • Laparoscopic is associated with less postoperative pain[307-312] • Mini-laparoscopy may be associated with less postoperative pain • Robotic associated with less postoperative pain than traditional laparoscopic Operative anesthesia: • Minimize or avoid induction opioids and minimize intraoperative maintenance opioids • Infiltration of local amide anesthetic at the surgical sites[313] Pharmacologic agents: • Dexamethasone 0.1-0.2 mg/kg IV given slowly preoperatively or at induction[314] • Acetaminophen 1000 mg IV if more than six hours since last dose and patient cannot get PO or PR, with a goal of administering a dose every six hours • Ketorolac 15 mg IV at closure, unless contraindicated or an NSAID was administered preoperatively	Operative anesthesia: • Opioid-free total intravenous anesthesia (TIVA) (e.g., propofol, dexmedetomidine, lidocaine and ketamine)[315] Regional anesthesia:[316-318] • Transversus abdominis plane (TAP) block (single shot or continuous infusion) • Quadratus lumborum (QL2 or TQL) block[319] • Erector spinae block[320] • Rectus sheath block[321] • Consider the use of liposomal bupivacaine for incisional and/or regional anesthesia/analgesia[322,323] • Consider instillation of IPLA[324,325] Pharmacologic agents: • Lidocaine 1.5 mg/kg IV bolus (max dose 150 mg) +/- 1-3 mg/kg/hr IV infusion[326-329] - It is recommended that the infusion be stopped if and when liposomal bupivacaine is administered • Esmolol loading dose of 0.5 mg/kg IV bolus over one minute followed by 0.01-0.05 mg/kg/min IV infusion[330,331] • Magnesium sulfate 30-50 mg/kg IV bolus followed by 6-20 mg/kg/hr IV infusion ***OR*** 4 g IV given over 30-60 minutes at the close of case[278,285,332,333]

Opioid-sparing Multimodal Analgesic Pathway for Hysterectomy *continued*

Consider for Intraoperative Use

For major open procedures or as adjunctive analgesia for patients who are anticipated to have difficult-to-manage postoperative pain, including opioid-dependent patients, patients with chronic pain, patients with a history of severe or refractory postoperative pain, and patients who request opioid-free surgery, consider use of the above multimodal agents and one or more of the following as clinically appropriate:

Pharmacologic agents:
- Ketamine 0.1-0.3 mg/kg IV bolus once pre-incision +/- ketamine 0.1-0.3 mg/kg/hr IV infusion[334-337]
- Dexmedetomidine 0.8-1 mcg/kg IV bolus + 0.2-0.8 mcg/kg/hr IV infusion[265,315,338-341]
- Catheter placement for continuous wound infusion with amide anesthetic

Regional analgesia:
- Neuraxial analgesia: spinal, thoracic epidural anesthesia (TEA) or combined spinal and epidural anesthesia (CSEA).[342] Epidural analgesia provides pain relief for patients undergoing laparoscopic hysterectomy, but it should be considered a reserve intervention because surgery is now often performed on an ambulatory basis and less invasive modalities are adequate for managing pain in most patients.
- For patients with thoracic epidural, consider administering a bolus prior to incision and/or running an infusion intraoperatively.

Postoperative Recommendations

- Acetaminophen 1 g PO every six to eight hours until pain is resolved. Use IV acetaminophen only for patients in whom oral and PR administration are contraindicated ***PLUS***
- Ketorolac 15 mg IV every six hours for 24-48 hours followed by
  - NSAID (ibuprofen 600 mg PO every six hours ***OR*** naproxen 500 mg PO every 12 hours) ***OR***
  - COX-2 NSAID (celecoxib 100-200 mg PO every 12 hours ***OR*** meloxicam 7.5-15 mg PO once daily) scheduled until pain is resolved
- Nonpharmacological interventions

Consider for Postoperative Use

- Gabapentin 300-600 mg PO one to three times daily ***OR*** pregabalin 75-150 mg PO one to two times daily (adjust for age, renal function)[343]
- Lidocaine 1-2 mg/kg/hr IV infusion[326-329]
  - Avoid if liposomal bupivacaine used or continuous wound infusion continued
- Dextromethorphan 40 mg PO three times a day for two days[286,299,300]
- Lidocaine 5% patch once daily, applied adjacent to incision (up to three patches)

For major open procedures or as adjunctive analgesia for patients who are anticipated to have difficult-to-manage postoperative pain, including opioid-dependent patients, patients with chronic pain, patients with a history of severe or refractory postoperative pain, and patients who request opioid-free surgery, consider use of the above multimodal agents and one or more of the following as clinically appropriate:

Pharmacologic agents:
- Ketamine 0.1-0.3 mg/kg IV bolus +/- 0.1-0.3 mg/kg/hr IV infusion for 24-48 hours[334-337]
- Dexmedetomidine 0.2-0.8 mcg/kg/hr IV infusion for up to 24 hours[265,338-340]
- Lidocaine 1-2 mg/kg/hr IV infusion for 24-48 hours (avoid if liposomal bupivacaine or other forms of wound infusion or epidural amide anesthetic are continued)

Regional Anesthesia:
- Continuous wound infusion with amide anesthetic
- Continued epidural adjunctive analgesia

Opioid-sparing Multimodal Analgesic Pathway for Hysterectomy *continued*

It is recommended that opioids be reserved for patients whose pain is not well controlled with nonopioid analgesia, that patients receiving opioid therapy be maintained on multimodal analgesic agents as clinically appropriate and that opioid monotherapy be avoided. It is recommended that patients receive several nonopioid analgesic interventions prior to use of an opioid for pain.

It is advised to initiate opioid treatment with:
- Oxycodone IR 2.5-10 mg PO every four to six hours as needed ***OR***
- Morphine IR 5-20 mg PO every four to six hours as needed

For pain not controlled with above opioid options, consider:
- Tapentadol IR 50-100 mg PO every six hours as needed
- Hydromorphone IR 2-6 mg PO every six hours as needed

For pain not controlled by oral opioids, if patient strict NPO, or for severe breakthrough pain, consider:
- Morphine 1-4 mg IV every four hours as needed ***OR***
- Hydromorphone 0.25-1 mg IV every three to four hours as needed

Discharge Recommendations	Consider for Prescription on Discharge
• Acetaminophen 1 g PO every six to eight hours until pain is resolved • NSAID (ibuprofen 600 mg PO every 6 hours ***OR*** naproxen 500 mg PO every 12 hours) ***OR*** • COX-2 NSAID (celecoxib 100-200 mg PO every 12 hours ***OR*** meloxicam 7.5-15 mg PO once daily) scheduled until pain is resolved	• Lidocaine 5% patch once daily, applied adjacent to incision (up to three patches) • Dextromethorphan 40 mg PO three times per day for two days[286,299,300] • For patients who benefited from gabapentinoid therapy while hospitalized, consider prescribing a five- to 10-day course of a gabapentinoid upon discharge. - It is suggested that the discharge dosing regimen match the inpatient dosing regimen. - For neuropathic or persistent postoperative pain, consider gradual titration to a dose of gabapentin 600-1200mg TID or pregabalin 150-225mg BID - It is recommended that concurrent use of gabapentinoids and opioids in the outpatient setting be avoided as it increases the risk of respiratory depression. • For opioid-naive patients, prescribe between zero and 15 tablets of oxycodone 5 mg (or other opioid monoproduct equivalent) for abdominal, or between zero and 10 tablets for vaginal or laparoscopic hysterectomy.

Managing Perioperative Pain in Gynecologic Patients Receiving MAT

NOTE: Many of the agents presented here are not appropriate for use in pregnancy.

1. The use of methadone, buprenorphine or naltrexone for the treatment of OUD may necessitate changes to usual perioperative pain management.
2. It is advised that the use of pharmacologic and nonpharmacologic alternatives to opioids be maximized in patients receiving MAT.
3. It is recommended that analgesia be offered to all patients receiving MAT who are in pain. A patient's usual dose of buprenorphine or methadone is generally inadequate for pain control.
   a. Splitting home doses of buprenorphine or methadone three times per day leverages the early analgesic effects of these medications; however, the analgesic effect is inadequate to address moderate or severe pain, and this approach may not always be logistically feasible.[344,345]
4. Strongly consider consulting anesthesia or pain medicine for the use of neuraxial or regional anesthetic techniques in patients with difficult-to-manage perioperative pain.
5. The following agents may be of particular value for the treatment of patients receiving MAT.
   a. It is recommended that any patient in pain receive scheduled acetaminophen and an NSAID, except when clinically contraindicated.
   b. 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 required.
   c. 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]).
   d. NMDA antagonists: Ketamine is the most potent nonopioid analgesic for opioid-tolerant patients. A brief infusion of 0.1-0.3 mg/kg IV over 15 minutes is followed by 0.1-0.3 mg/kg/hr IV infusion. In addition, magnesium is an NMDA receptor antagonist with analgesic and opioid-sparing effects (e.g., 30-50 mg/kg IV bolus followed by 6-20 mg/kg/hr IV infusion).
   e. IV lidocaine: A bolus of 1.5 mg/kg is followed by 1-3 mg/kg/hr infusion. Contraindications include cardiac dysrhythmias.
6. No patient should be denied adequate pain relief. It is recommended that patients on MAT whose pain is not controlled with nonopioid approaches be offered opioid analgesia with a short-acting agent.
   a. Due to cross-tolerance and increased pain sensitivity, it is advised that higher-than-typical doses of opioids will generally be required to treat pain in patients on stable regimens of methadone or buprenorphine.
   b. As for any patient receiving opioids, close monitoring is advised.
      i. 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.110
      ii. 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, clinicians are advised to select agents with affinity for the μ-opioid receptor sufficient to displace buprenorphine, such as fentanyl, sufentanil or hydromorphone.
      iii. While it is possible to treat acute pain with additional buprenorphine doses, if an opioid is required it is generally preferable to treat acute pain in patients maintained on buprenorphine with a short-acting opioid and not alter the patient's usual buprenorphine dosage.
7. 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 outcompete naltrexone at the opioid receptor. It is advised that patients be closely monitored, at minimum with pulse oximetry and telemetry, to prevent over-sedation and unintentional overdose.

Opioid-Sparing Multimodal Analgesic Pathway for Cesarean Delivery

Preoperative Recommendations

- Acetaminophen 1000 mg PO once

Consider for Preoperative Use

- COX-2 NSAID (celecoxib 200-400 mg PO once ***OR*** meloxicam 7.5-15 mg PO once)
- Magnesium sulphate 50 mg/kg slow IV bolus
- For patients with marked anxiety, consider
  - Nitrous oxide 30-50% via patient-controlled mask
  - Melatonin 6 mg PO once[301-304]
  - Clonidine 0.1 mg PO once[265,305,306]

NOTE: It is recommended that preoperative oral agents listed be administered 30-90 minutes prior to procedure.

Intraoperative Recommendations

Operative technique:
- Transverse incisions associated with less postoperative pain than vertical incisions.
  - Joel-Cohen associated with less postoperative pain than Pfannenstiel

Operative anesthesia:
- Minimize or avoid induction opioids and minimize intraoperative maintenance opioids
- Infiltration of amide anesthetic at the surgical site before incision
- Neuraxial anesthesia (spinal, epidural, CSEA)
  - Intrathecal morphine 50-150 mcg or
  - Epidural morphine 1-3 mg
    - Consider sufentanil and morphine as epidural agents

Pharmacologic agents:
- Dexamethasone 0.1-0.2 mg/kg IV given slowly preoperatively or at induction[314]
- Ketorolac 15-30 mg IV after peritoneum is closed, unless contraindicated or an NSAID was administered preoperatively

Consider for Intraoperative Use

Operative anesthesia:
- Adjuvant intrathecal clonidine 75-150 mcg
- Adjuvant intrathecal magnesium 0.1 mL preservative-free 10% magnesium sulfate (10 mg)
- Adjuvant intrathecal dexmedetomidine 0.5 µg/kg[346]
- If neuraxial anesthesia is contraindicated, consider opioid-free TIVA (e.g., propofol, dexmedetomidine, lidocaine and ketamine)[315]
- Retain access for continued postoperative neuraxial analgesia/placement of catheter for PCEA

Regional anesthesia:[316-318]
- Place catheter for CWI
- TAP block
  - Consider use of liposomal bupivacaine

Pharmacologic agents:
- Magnesium sulfate 30-50 mg/kg IV bolus followed by 6-20 mg/kg/hr IV infusion ***OR*** 4 g IV given over 30-60 minutes at the close of case[277-281,283,284]

Postoperative Recommendations

- Acetaminophen 1 g PO every six to eight hours until pain is resolved. Use IV acetaminophen only for patients in whom oral and per rectum (PR) administration are contraindicated.
- Ketorolac 15 mg IV every six hours for 24-48 hours followed by
  - NSAID (ibuprofen 600 mg PO every 6 hours ***OR*** naproxen 500 mg PO every 12 hours) ***OR***
  - COX-2 NSAID (celecoxib 100-200 mg PO every 12 hours ***OR*** meloxicam 7.5-15 mg PO once daily) scheduled until pain is resolved
- Lidocaine 5% patch once daily, applied adjacent to incision (up to three patches)
- Nonpharmacological interventions

Opioid-sparing Multimodal Analgesic Pathway for Cesarean Delivery *continued*

It is recommended that opioids be reserved for patients whose pain is not well controlled with nonopioid analgesia, that patients receiving opioid therapy be maintained on multimodal analgesic agents as clinically appropriate and that opioid monotherapy be avoided.

Initiate opioid treatment with:
- Oxycodone IR 2.5-10 mg PO every four to six hours as needed ***OR***
- Morphine IR 5-20 mg PO every four to six hours as needed

For pain not controlled with above opioid options, consider:
- Tapentadol IR 50-100 mg PO every six hours as needed
- Hydromorphone IR 2-6 mg PO every six hours as needed

For pain not controlled by oral opioids, if patient strict NPO or for severe breakthrough pain, consider:
- Morphine 1-4 mg IV every four hours as needed ***OR***
- Hydromorphone 0.25-1 mg IV every three to four hours as needed
- PCA opioid analgesia is not recommended

Discharge Recommendations	Consider for Prescription on Discharge
• Acetaminophen 1 g PO every six to eight hours until pain is resolved • NSAID (ibuprofen 600 mg PO every 6 hours ***OR*** naproxen 500 mg PO every 12 hours) ***OR*** • COX-2 NSAID (celecoxib 100-200 mg PO every 12 hours ***OR*** meloxicam 7.5-15 mg PO once daily) scheduled until pain is resolved	• Lidocaine 5% patch once daily, applied adjacent to incision (up to three patches) • For opioid-naive patients, prescribe between zero and 20 tablets of oxycodone 5 mg (or other opioid monoproduct equivalent) • The decision to prescribe an opioid and the dose and duration of opioid therapy can be a shared decision with the patient. A patient's opioid use in the 24 hours prior to discharge, level of discomfort, medical and behavioral health comorbidities and preferences may guide discharge prescribing.

Managing Perioperative Pain in Opioid-Dependent Patients Undergoing Cesarean Delivery

In addition to the recommendations above, consider use of the following multimodal agents for patients who are anticipated to have difficult-to-manage postoperative pain, including opioid-dependent patients, patients with chronic pain, patients with a history of severe or refractory postoperative pain, and patients who request opioid-free surgery.

1. For patients on MAT, continue the patient's preoperative methadone or buprenorphine regimen throughout the perioperative period. Patients on chronic opioid therapy should be continued on their regimens.
2. **Preoperative:**
   a. Gabapentin 300-600 mg PO once ***OR*** pregabalin 75-150 mg PO once (adjust the dose for age, renal function)[297,298]
3. **Intraoperative:**
   a. Pharmacologic therapy:
      - Ketamine 0.1-0.3 mg/kg IV bolus once pre-incision +/- ketamine 0.1-0.3 mg/kg/hr IV infusion[276,334-337,347]
      - Dexmedetomidine 0.8-1 mcg/kg IV bolus + 0.2-0.8 mcg/kg/hr IV infusion[286,315,338-341]
      - Lidocaine 1-2 mg/kg IV bolus (max dose 150 mg) +/- 1-3 mg/kg/hr IV infusion[326-329]
        (It is recommended that infusion be stopped if liposomal bupivacaine is administered.)
   b. Regional anesthesia: If neuraxial anesthesia is contraindicated or fails, consider[316-318]
      - TAP block (single shot or continuous infusion)[348]
      - Quadratus lumborum (QL1) block[319]
      - Ilioinguinal-Iliohypogastric (II-IH) nerve block
      - ESP block[320]
      - Rectus sheath[321]
      - Consider the use of liposomal bupivacaine for incisional anesthesia/analgesia[322,323]
      - Consider instillation of IPLA[250,324]
4. **Postoperative:**
   a. Pharmacologic Agents:
      - Ketamine 0.1-0.3 mg/kg IV bolus +/- 0.1-0.3 mg/kg/hr IV infusion for 24-48 hours[334-337]
      - Dexmedetomidine 0.2-0.8 mcg/kg/hr IV infusion for up to 24 hours[265,338-340]
      - Lidocaine 1-2 mg/kg/hr IV infusion for 24-48 hours (avoid if liposomal bupivacaine or other forms of wound infusion or epidural amide anesthetic are continued)
      - Gabapentin 300-600 mg PO one to three times daily OR pregabalin 75-150 mg PO one to two times daily (adjust for age, renal function)[343]
   b. Regional Anesthesia:
      - Continuous wound infusion with amide anesthetic
      - Continued epidural adjunctive analgesia
      - Patient controlled epidural analgesia
      - Lidocaine 5% patch once daily, applied adjacent to incision (up to three patches)
5. **Discharge prescribing**:
   a. Consider gabapentin 300-600 mg PO one to three times daily OR pregabalin 75-150 mg PO one to two times daily (adjust for age, renal function) at discharge.[71,343] Exercise caution when combined with patient's pre-existing opioid agonist therapy.

Multimodal Analgesic Pathways for Common Gynecologic Conditions

NOTE: The doses suggested below for pharmacologic agents are starting doses only and do not account for patient-specific considerations such as renal or hepatic impairment, geriatric dosing requirements, drug interactions and contraindications in pregnancy. Not all agent options are listed under each drug class. See "Nonopioid Pharmacologic Agents for Multimodal Analgesia" in **SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE**, for more information regarding evidence, agents, dosing, monitoring and other considerations. Many patients benefit from scheduled analgesics (i.e., around-the-clock acetaminophen + NSAID) for 48-72 hours, then switching to as needed use once acute pain has subsided.

Management of Chronic Pelvic Pain (CPP)[72]

Diagnosis and treatment of underlying pathology is recommended. Causes of CPP include a broad range of gynecological, neuromusculoskeletal and psychosocial disorders. For patients for whom no clear inciting cause of pain is identified, a multimodal approach to pain control that utilizes both nonpharmacologic and nonopioid pharmacologic therapies is advised. ACOG Practice Bulletin 218 states that opioids are not recommended for the treatment of CPP and provides detailed information on diagnosis and treatment of CPP.

Nonpharmacologic Treatments[349-351]

- Psychoeducational approaches[352]
- Cognitive behavioral therapy (CBT) or other behavioral health care, as indicated[353,354]
- Mindfulness-based therapy[355]
- Sex therapy[72]
- Dietary and environmental modifications
- Complementary and alternative medicine approaches such as acupuncture,[356] relaxation techniques, meditation and yoga[357]
- Pelvic floor physical therapy[72,358,359]
  - If pain is reproducible on palpation or contraction of pelvic floor, consider specialized pelvic floor physical therapy by a practitioner with expertise in CPP.
- Dry needling of trigger points[360]
- Noninvasive neuromodulation[361] with transcutaneous nerve stimulation (TENS)[362] unit
- Medical grade vaginal dilators
  - Consider in dyspareunia
- Referral to pain specialist for neuromodulation such as sacral nerve stimulation (SNS), spinal cord stimulation (SCS) or peripheral nerve stimulation (PNS).[363]
- Avoid surgery.[353]

Pharmacologic Treatments

- NSAIDs:
  - Ibuprofen 400-800 mg 4x daily
  - Celecoxib 200 mg 2x daily
- Acetaminophen 500-1000 mg PO 3-4x daily
- If rectal, genital or perineal pain present consider a topical compounded agent:
  - 1-2% amitriptyline/0.5-1% ketamine gel or cream, applied 1-3x daily[364]
- SNRIs or tricyclic antidepressants (TCAs):[72,365]
  - Amitriptyline/nortriptyline 10-25 mg PO once daily
  - Duloxetine 30 mg PO once daily or venlafaxine 37.5 mg PO once daily
  - These options are indicated for neuropathic pain or central sensitization in CPP
- Gabapentinoids:[72]
  - Gabapentin[366] 100-300 mg PO 1-3x daily or pregabalin 50-75 mg PO 1-2x daily
- Muscle relaxants:
  - Cyclobenzaprine 5-10 mg PO 1-3x daily
  - Tizanidine 2-4 mg PO 2-4x daily
- Hormonal treatments:[353,367,368]
  - Oral contraceptive pills[353]
  - Progestin-containing IUD
- Botulinum toxin injection[72]
  - For myofascial pelvic pain refractory to physical therapy
- Trigger point injections with steroids and anesthetic[72]
  - If myofascial dysfunction and/or presence of myofascial trigger points.
- Nerve blocks, including pudendal nerve block, sympathetic blocks, ganglion impar, hypogastric block, anterior cutaneous nerve block or medial cluneal nerve block.

Management of Pain in Patients with Vulvodynia[369-375]

Infectious, inflammatory, neurologic, neoplastic and other causes of vulvar pain should be excluded. Nonpharmacologic treatments and nonopioid medications may be of benefit, though scant evidence exists to assess the efficacy of any systemic pharmacotherapeutic agent or nonpharmacologic intervention for pain associated with vulvodynia. Pharmacologic treatment may be guided by general recommendations for management of chronic pain. No evidence supports the use of opioid analgesia for vulvodynia, and multimodal nonopioid and nonpharmacologic therapy is recommended.

Nonpharmacologic Treatments

- Vulvar care measures:
  - Wear 100% cotton underwear (no underwear at night)
  - Avoid vulvar irritants (perfumes, dyes, shampoos, detergents) and douching
  - Use mild soaps for bathing, without applying it to the vulva
  - Clean the vulva with water only
  - Avoid the use of hair dryers on the vulvar area
  - Pat the area dry after bathing, and apply a preservative-free emollient (such as vegetable oil or plain petrolatum) topically to hold moisture in the skin and improve the barrier function
  - Switch to 100% cotton menstrual pads (if regular pads are irritating)
  - Use adequate lubrication for intercourse
  - Apply cool gel packs to the vulvar area
  - Rinse and pat the vulva dry after urination
- Physical therapy[376]
  - If pain is reproducible on palpation or appears to have a muscular, structural or functional component, physical therapy by a practitioner with expertise in CPP may employ:
    - Biofeedback
    - Manipulation of soft tissue and/or joint
    - Therapeutic ultrasonography
    - TENS
- CBT,[376] individual or couples' psychotherapy, sex therapy
- Consider surgery for provoked vestibulodynia if all other therapies fail[372,376]
  - Vestibulectomy with vaginal advancement
  - Modified vestibulectomy (only the superficial painful tissue is removed and there is no vaginal advancement)
- Consider referral to pain specialist for nerve blocks, including:
  - Ganglion impar
  - Pudendal and/or caudal blocks of local anesthetic, or local anesthetic and steroid
  - Limited studies of multilevel nerve blocks (subcutaneous, pudendal, caudal) demonstrate efficacy

Pharmacologic Treatments

- NSAIDs:
  - Ibuprofen 400-800 mg PO 4x daily
  - Celecoxib 200 mg PO 2x daily
- Acetaminophen 500-1000 mg PO 3-4x daily
- Anticonvulsants:
  - Gabapentin 100-300 mg PO 1-3x daily[376]
  - Pregabalin 50-75 mg PO 1-2x daily
  - Lamotrigine 25 mg PO once daily[377]
  - Topiramate 25 mg PO once daily[378]
  - Oxcarbamazepine 150 mg PO 2x daily
- SNRIs
  - Duloxetine 30 mg PO once daily
  - Venlafaxine 37.5 mg PO once daily
  - Milnacipran 12.5 mg PO 1-2x daily[379]
- Topical medications*
  - Topical hormonal (estrogen)
  - Topical lidocaine 5% gel
  - Topical compounded anticonvulsants (gabapentin) or antidepressants
  - Topical baclofen 5%
- Vaginal diazepam 10 mg 1-2x daily
- Injections
  - Botulinum toxin A[380]
  - Steroid
  - Trigger point injections with steroid and anesthetic

*NOTE that ointments are usually better tolerated than creams; creams contain more preservatives and stabilizers than ointments and may produce burning on application.

Management of Pain in Patients with Primary Dysmenorrhea[369-375]

Secondary causes of dysmenorrhea, including endometriosis, adenomyosis or uterine fibroids, should be excluded. Per ACOG committee opinion 760, opioids (including tramadol) should not be prescribed to adolescents with dysmenorrhea.

Nonpharmacologic Treatments	Pharmacologic Treatments
• Exercise,[381,382] yoga • Heat[383,384] • Acupressure/acupuncture • High-frequency TENS[385] • No evidence supports use of surgical interventions (uterine nerve ablation, presacral neurectomy)	• NSAID386 + acetaminophen - Ibuprofen 400-800 mg PO 4x daily + acetaminophen 500-1000 mg PO 3-4x daily - Most effective when started 1-2 days prior to onset of menses and continued through the first three days of bleeding.[387] - Addition of caffeine 130 mg PO to acetaminophen 1 g may enhance efficacy[388] • Antispasmodic (if cramping component)389 - Dicyclomine 10-20 mg PO 4x daily • Hormonal agents - Oral contraceptive pills - Hormonal IUD - Patients with endometriosis who have pain refractory to conservative surgical therapy and suppressive hormonal therapy often benefit from at least six months of gonadotropin-releasing hormone (GnRH) agonist therapy with add-back medicine • Dietary supplements (limited supporting evidence)[73,390] - Vitamins D,[390,391] E,[390,392,393] B1,[394] B6 - Zinc sulphate - Herbs (ginger, fenugreek, valerian, fennel,[395,396] chamomile and zataria[397]) - Fish oil[392] - Green tea[398]

Pain Associated with Ovarian Cyst

Usual evaluation to exclude endometrioma, malignancy, teratoma and cystadenoma. For functional ovarian cyst, watchful waiting and reassurance are advised. For patients with pain, nonpharmacologic and nonopioid pharmacologic treatments are recommended and use of opioid analgesia is strongly discouraged.

Nonpharmacologic Treatments	Pharmacologic Treatments

• Heat
• Massage
• Relaxation techniques
• Exercise (yoga)
• Maintain healthy body weight
• If cystectomy[399] or oophorectomy is indicated, use of minimally invasive procedures is advised when feasible.
• Patient education
	• NSAIDs
	  - Ibuprofen 400 mg PO 4x daily
	  - Celecoxib 200 mg PO 2x daily
	• Acetaminophen 500-1000 mg PO 3-4x daily
	• Consider use of hormonal agents for prevention of recurrence.

Pain Associated with with First-Trimester Miscarriage[400]

Management of miscarriage should incorporate the preferences of the patient. Nonpharmacologic and nonopioid pharmacologic treatments are recommended, and use of opioid analgesia is strongly discouraged.

Nonpharmacologic Treatments	Pharmacologic Treatments

• Patient education, reassurance
• Consider screening for depression, anxiety or grief reactions and referral for behavioral health evaluation and care if appropriate.
• Heat
• Massage
• Relaxation techniques
• Exercise
	• NSAIDs:
	  - Ibuprofen 400 mg PO 4x daily
	  - Celecoxib 200 mg PO 2x daily
	• Acetaminophen 500-1000 mg PO 3-4x daily
	• Resolution of incomplete miscarriage, fetal demise or anembryonic pregnancy may be hastened with certain agents, alleviating associated physical pain.
	  - Misoprostol 800 mcg intravaginal x1, may repeat up to three doses
	  - Methylergonovine 0.2 mg PO 3-4x daily (max seven days)
	• If dilation and curettage (D and C) is indicated, it is advised that patients not be routinely prescribed an opioid. A scheduled regimen of NSAID and acetaminophen provides adequate analgesia for the majority of patients.

Multimodal Pain Management in Nonsurgical Obstetric Care

Management of Pain in Vaginal Labor and Delivery

Obstetrician-gynecologists should avoid use of opioids for management of labor pain except where neuraxial modes of analgesia are unavailable or contraindicated. Opioids have been found to have minimal effects on maternal pain scores, provide unreliable analgesia and frequently cause sedation, nausea and vomiting. A Cochrane review found no opioid more effective than another in managing labor pain and found that all were associated with significant sedation, nausea and vomiting. Opioids may also decrease fetal heart rate variability, limiting interpretation of fetal heart rate tracing.

Nonpharmacologic Treatments[401]	Pharmacologic Treatments

• Continuous labor support
• Warm water baths[402] and/or birth[403]
• Maternal movement and positioning
• Massage
• Pain-relief methods without prospective studies include:[404]
  - acupuncture
  - relaxation
  - breathing
  - visualization
  - aromatherapy
  - massage
• Research on the value of TENS in labor is equivocal.[405,406] Some studies suggest benefit in the first stage of labor or in combination with other forms of analgesia.[407]
	• Neuraxial analgesia has been shown to provide superior analgesia to parenteral opioids for labor pain management[408,409]
	  - No difference between continuous- infusion vs. intermittent bolus[410]
	• While not as effective as neuraxial anesthesia for management of labor pain,[411] nitrous oxide has been used for decades and does offer some advantages[412]
	  - No additional monitoring
	  - Allows patient to be mobile and control
	  - Can be safely used with other analgesia
	  - Rapid onset and elimination

Management of Pain after Vaginal Delivery[71]

Pain after vaginal birth can interfere with the ability to care for oneself and one's infant. Nonpharmacologic and pharmacologic therapies are important components of postpartum management of pain caused by perineal lacerations, uterine contractions or nipple pain. It is advised that obstetricians not routinely prescribe opioids for patients after vaginal delivery due to the short-term risks of impairment and sedation for both patient and neonate and the long-term risk of misuse, dependence and addiction. ACOG provides guidance in postpartum pain management **HERE.**

Nonpharmacologic Treatments[401]	Pharmacologic Treatments
• Breast engorgement - More frequent breastfeeding - Lactation specialist consultation - Assessment of infant latch - Cold packs - Fit of pump flanges - Application of breastmilk + breastshield • Uterine cramping - Application of heat • Perineal pain - Cold packs[413]	• Breast engorgement[414,415] - Acetaminophen 500-1000 mg PO 3-4x daily + ibuprofen 400-800 mg PO 4x daily - Consider topical lanolin,[416] though evidence is weak • Uterine cramping - Ibuprofen 400-800 mg PO 4x daily • Perineal pain - Topical anesthetics (benzocaine spray) - Acetaminophen 500-1000 mg PO 3-4x daily + ibuprofen 400-800 mg PO 4x daily

Nonopioid Pharmacologic Agents for Multimodal Analgesia

NOTE: Agents listed below are organized alphabetically by drug type. Many drug types and agents are used both in the outpatient and surgical settings; the evidence, dosing and considerations specific to surgery are contained in boxes within each agent description.

(TABLE 8)

Multimodal Analgesic Medications

Type	Example
Acetylcholine release inhibitor	Botulinum toxin A
Alpha-2 adrenergic agonists	Clonidine, dexmedetomidine
Amide anesthetics	Benzocaine (topical only), bupivacaine, lidocaine, liposomal bupivacaine, ropivacaine
Amine reuptake inhibitors	Amitriptyline, duloxetine, nortriptyline, venlafaxine
Anticonvulsants	Lamotrigine, oxcarbazepine, topiramate
Anxiolytics	Benzodiazepines, clonidine, gabapentin, melatonin
Beta blockers	Esmolol
Central prostaglandin synthesis inhibitor	Acetaminophen
Gabapentinoids	Gabapentin, pregabalin
Glucocorticoids	Dexamethasone, triamcinolone
Hormonal agents	Medroxyprogesterone, GnRH agonists, GnRH antagonists, intrauterine systems, oral contraceptives (estrogen and progesterone combinations, or progesterone alone)
Muscle relaxants/antispasmodics	Cyclobenzaprine, dicyclomine, tizanidine
NMDA receptor antagonists	Dextromethorphan, ketamine, magnesium
NSAIDs	(Cox-1, 2, 3 inhibitors) Celecoxib, ibuprofen, ketorolac, meloxicam, naproxen
Other topical agents	Amitriptyline/ketamine gel, baclofen topical, diazepam intravaginal tablets, gabapentin gel

Acetylcholine Release Inhibitor

BOTULINUM TOXIN A

EVIDENCE: The evidence is inconclusive regarding the value of botulinum toxin injections for myofascial pain syndromes from all sources. Their use is reserved for the treatment of myofascial pelvic pain refractory to physical therapy.[417,418]

MECHANISM OF ACTION: A neurotoxin produced by Clostridium botulinum, which appears to affect the presynaptic membrane of the neuromuscular junction, preventing release of acetylcholine and resulting in a state of denervation.

AGENTS AND DOSING: OnabotulinumtoxinA 100-300 IU of Botox diluted in normal saline, often administered in multiple injections; repeat injections every few months may be required for sustained effect.

CONTRAINDICATIONS AND CAUTIONS: Systemic toxicity, though rare, can occur including dysphagia and breathing difficulties.

PREGNANCY AND LACTATION CONSIDERATIONS: Limited human data in pregnancy—animal data suggest low risk. No human data in breastfeeding—probably compatible. Evidence in pregnancy and lactation is extremely limited and therefore use is often avoided.

Alpha-2 Adrenergic Agonists

CLONIDINE

EVIDENCE: A meta-analysis of nearly 1800 mixed surgical patients receiving either clonidine or dexmedetomidine perioperatively found that clonidine reduced opioid requirements 12-24 hours postoperatively, with an overall decrease in opioid requirements of 25%.[265] Premedication with oral clonidine prolongs the duration of effect of bupivacaine spinal anesthesia, can significantly decrease cumulative MME 12 and 24 hours after surgery and decrease the incidence of early postoperative nausea and vomiting (PONV).[265,272-275] Epidural and spinal clonidine also enhance the quality and duration of neuraxial anesthesia and reduce the required dose of local anesthetic and other neuraxial additives, including opioids.[246] Oral clonidine also helps alleviate opioid withdrawal symptoms in patients with difficult-to-manage pain who are receiving MAT or COT.

MECHANISM OF ACTION: Stimulates alpha 2-adrenergic receptors in the brain, resulting in reduced sympathetic outflow from the CNS. It is less selective for alpha-2 adrenoreceptors than dexmedetomidine, which may account for the less pronounced opioid-sparing effect when the two drugs are compared.

DOSING: IT dosing typically starts at 15 mcg, alone or in combination with other agents, and may be increased up to 150 mcg. Preoperative oral doses are between 0.1 and 0.2 mg administered 30-90 minutes prior to surgery. Dosing for adjunct agents in opioid withdrawal is 0.1-0.3 mg PO every six to eight hours; may transition to an equivalent dose of a transdermal patch once a stable oral dose is established.

CONTRAINDICATIONS AND CAUTIONS: Epidural clonidine is not recommended for patients with severe cardiovascular disease or hemodynamic instability.

MONITORING: Monitor for bradycardia and hypotension. Abrupt discontinuation after prolonged use may result in withdrawal symptoms, including agitation, headache and rebound hypertension.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Limited human data in pregnancy—animal data suggest risk.* No reports linking the use of clonidine with congenital defects have been located. The drug has been used during all trimesters, but experience during the first trimester is limited. Adverse fetal effects attributable to clonidine have not been observed. *Limited human data in breastfeeding—probably compatible.* Clonidine is secreted into breast milk, but hypotension was not observed in the nursing infant.

NOTE: See below for description of clonidine as used for anxiolysis.

DEXMEDETOMIDINE

EVIDENCE: The meta-analysis cited above found that dexmedetomidine also produced a statistically significant decrease in opioid consumption and postoperative pain intensity at 24 hours, as well as early PONV.[265] While no large-scale clinical trials have been conducted, the current body of evidence suggests that dexmedetomidine is suitable for use as an adjuvant analgesic at all perioperative stages via multiple administration routes (IV, IN, intrathecal), particularly in conjunction with regional anesthetics and for patients who are on COT or MAT.[264] One meta-analysis found IV dexmedetomidine superior to placebo in attenuating the incidence of

PONV, postoperative shivering, pruritus, as well as the pain scores in patients undergoing gynecological surgeries.[266] One study compared IV dexmedetomidine to IV lidocaine. Both dexmedetomidine and lidocaine were found to be a useful adjuvant to general anesthesia in patients undergoing abdominal gynecological surgeries. However, dexmedetomidine had a better sparing effect on intraoperative anesthetic consumption and longer time to the first postoperative analgesic demand than that of lidocaine with no significant difference between both agents on intraoperative analgesic demand.[267] Another study compared the combination of IV lidocaine and IV dexmedetomidine to placebo or either alone in patients undergoing abdominal hysterectomy and found the combination to be especially effective, significantly improving postoperative pain and enhanced recovery of bowel function.[268] While studies are more limited during cesarean delivery, IV dexmedetomidine has been found to efficiently attenuate the maternal cardiovascular response during cesarean delivery and does not affect Apgar score of the neonate, making it a safe option for this procedure as well.[269] Some studies have found a benefit on pain control too, with IV dexmedetomidine demonstrating better neonatal Apgar scores, postoperative analgesia, and decreased catecholamine release when compared to IV remifentanil in patients undergoing elective cesarean delivery under general anesthesia.[270,271] Overall, studies have demonstrated that IV dexmedetomidine elicits opioid-sparing effects, improves pain control and minimizes opioid-related side effects, most notably when used in the inpatient perioperative setting.[339,340] In conjunction with regional anesthetics, dexmedetomidine increases the anesthetic's duration of effect and prolongs analgesia.[420,421] While no studies have tested clonidine and dexmedetomidine head-to-head, dexmedetomidine appears to have a greater effect on postoperative morphine consumption and postoperative pain.

MECHANISM OF ACTION: Relatively selective alpha-2 adrenergic agonist with anesthetic and sedative properties, which are thought to be due to the activation of G-proteins by alpha2a-adrenoceptors in the brainstem, resulting in inhibition of norepinephrine release.

DOSING: Dexmedetomidine 0.2-0.8 mcg/kg/hr continuous IV infusion, though dose may be increased further based on the level of sedation and side effects. A loading IV infusion of 0.48-1 mcg/kg over 10 minutes may be considered but is typically avoided due to the risk of bradycardia; use additional caution if administering dexmedetomidine bolus with other medication boluses that may affect hemodynamics (i.e., ketamine, esmolol, lidocaine). Dexmedetomidine 2-10 mcg IT added to spinal anesthesia.

CONTRAINDICATIONS AND CAUTIONS: Use dexmedetomidine with caution in patients with advanced heart block or severe ventricular dysfunction. Bradycardia and hypotension may be more pronounced in the elderly and in those with hypovolemia; dosage reduction is recommended. Caution when co-administering multiple bolus medications at induction, particularly those that affect hemodynamics.

SPECIAL CONSIDERATIONS: Clinicians are advised to monitor for potential adverse effects, such as hypotension and bradycardia. While a dexmedetomidine infusion may be continued postoperatively, regardless of the patient's extubation status, most hospital policies require patients on infusions to be monitored in an intensive care setting.

MONITORING: Assess the patient's level of sedation, heart rate and blood pressure.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Limited human data in pregnancy—animal data suggest moderate risk.* The human pregnancy experience with dexmedetomidine is limited to short-term use immediately before or during delivery. The drug crosses the human placenta at term. Some evidence supports off-label use of dexmedetomidine might be beneficial in providing pain relief for laboring patients unwilling or unable to receive neuraxial analgesia. However, newborn toxicity, such as hypotension and sedation, is a potential concern though unfounded in recent studies. Moreover, dexmedetomidine may increase uterine contractions and this property should be considered if the drug is used during pregnancy. *No human data in breastfeeding—probably compatible.* It is unknown if dexmedetomidine is excreted in breast milk. The relatively low molecular weight suggests that it would be, but effects are unknown.

Amide Anesthetics

BENZOCAINE TOPICAL, LIDOCAINE TOPICAL

EVIDENCE: A comprehensive review of topically applied anesthetics for perineal pain after childbirth did not find evidence compelling, but acknowledged that use is low risk and embraced by both providers and patients.[422] Topical local anesthetics also appear to convey a mild antimicrobial effect, an added benefit of using these agents in the postpartum period.[423,424] Due to the relatively low risk associated with topical medications, the ability to transition these treatments to the outpatient setting and the availability of over-the-counter products, topical lidocaine transdermal patches and EMLA cream (or similar local anesthetic topicals) can be a reasonable option in most postpartum and discharge analgesic plans. Another topical anesthetic commonly used in the postpartum period is benzocaine 20% spray.

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

DOSING:

Lidocaine patches: Apply one to three patches to the site of pain once daily. It is advised that patches only be applied to intact skin. While the manufacturer recommends removing the patch after 12 hours, several small studies have validated the safety of wearing lidocaine patches for up to 24 hours prior to replacement.

Eutectic mixture of local anesthetics (EMLA) topical: Apply 2 g of cream topically per 10 cm^2 of skin and cover with an occlusive dressing for at least two hours. Benzocaine 20% spray apply to affected area one spray up to four times daily as needed.

MONITORING: Watch for skin irritation and burning.

DISCHARGE: Lidocaine patches may be prescribed upon discharge. If the prescription-strength patches (lidocaine 5%) are cost prohibitive or not covered by insurance, counsel patients regarding the over-the-counter availability of lidocaine 4% patches. Benzocaine 20% spray is also available over the counter.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Compatible in pregnancy (lidocaine). Limited human data in pregnanc—probably compatible (benzocaine).* Lidocaine and its metabolites cross the placenta and can be detected in the fetal circulation following injection. The amount of lidocaine absorbed topically varies by dose administered, duration of exposure and site of application, but is overall considered safe in pregnancy. There are more than 50 over-the-counter products that contain benzocaine, a number suggesting wide use of this anesthetic. There is no evidence that topical use of this drug class is associated with any aspect of developmental toxicity. Nevertheless, the best course is to avoid use on mucous membranes or damaged skin during pregnancy. *No human data in breastfeeding—probably compatible (benzocaine). Limited human data in breastfeeding—probably compatible (lidocaine).*

TRIGGER POINT INJECTIONS OF LOCAL ANESTHETIC

EVIDENCE: Trigger point injections of anesthetic, in isolation or in combination with other treatment modalities, are recommended by ACOG to improve pain and functional ability in patients with myofascial chronic pelvic pain. Limited evidence supports the use as a safe option that can provide immediate relief and be repeated.[425-428] There is also limited evidence in the benefit of trigger point injections in vulvodynia; a small study of multilevel injections resulted in improvement of pain.[429]

SPECIAL CONSIDERATIONS: May require repeated doses for full benefit. Evidence that trigger point injections are beneficial regardless of the injectant used (anesthetic, saline, steroid) raises the possibility that needle insertion itself may produce a strong placebo effect or be effective on its own.[427]

PREGNANCY AND LACTATION CONSIDERATIONS: See information above.

CONTINUOUS WOUND INFUSION OF LOCAL ANESTHETIC:

EVIDENCE: When compared to placebo, a continuous wound infusion of ropivacaine 0.2% following cesarean delivery was found to reduce postoperative morphine consumption significantly in the first six hours following surgery.[240] A study of multi-orifice continuous wound infusion of ropivacaine for 48 hours following cesarean delivery was associated with better analgesia, lower incidence of side effects, less need for nursing care, and shorter duration of stay when compared with epidural boluses of morphine.[241] Another study in patients undergoing cesarean delivery found that ropivacaine infused continuously via an elastomeric pump infuser was found to increase the duration and effect of post-cesarean analgesia comparable to patients that received IT morphine.[242] However a similar study comparing ropivacaine continuous wound infusion to placebo following cesarean delivery found no difference in outcomes.[430] Another study with ropivacaine 0.2% found a similar lack of compelling results.[431] Additional studies have been aimed at the placement of the catheter, finding continuous wound infusion for 48 hours after cesarean delivery with ropivacaine 0.2% administered below the fascia results in better analgesia when compared with administration above the fascia. Bupivacaine has also been studied in continuous wound infusion.[432] A small randomized trial of continuous wound infusion with subcutaneous bupivacaine 0.25% for 48 hours following cesarean delivery found no difference in pain scores when compared to placebo, but narcotic requirements to produce this amount of pain relief were significantly less in the bupivacaine infusion group.[433] A retrospective chart review that looked at the addition of bupivacaine continuous wound infusion to standard multimodal therapy and neuraxial morphine found that addition of the bupivacaine led to decreased opioid consumption on days one and two, but not thereafter, and pain scores did not differ between the two groups.[434] A study comparing bupivacaine continuous epidural infusion versus bupivacaine continuous surgical wound infiltration found epidural infusion to provide significantly lower pain scores with mobilization.[435] A 2016 meta-analysis including studies of both continuous and single-shot local wound infiltration for post-cesarean delivery analgesia found that local anesthetic wound infiltration reduces postoperative opioid consumption but had minimal effect on pain scores and did not reduce opioid-related side effects.[436] As the literature is currently mixed on benefit, there is not a strong recommendation to routinely use continuous wound infusion of local anesthetics following cesarean delivery, but CWI can be considered as part of the multimodal postoperative analgesia plan for select patients, particularly those with chronic pain, those who are opioid-dependent and those who are not candidates for neuraxial opioids.

DOSING: Ropivacaine and bupivacaine are the most commonly studied agents for continuous wound infusion following cesarean delivery. Following a bolus, an infusion of 5-10 mL/hr (ropivacaine 2 mg/mL) for up to 48 hours. Following a bolus, an infusion of 10 mL/hr (bupivacaine 0.25%) for up to 48 hours.

PREGNANCY AND LACTATION CONSIDERATIONS: See information below.

INTRAPERITONEAL INSTILLATION OF LOCAL ANESTHETIC (IPLA):[250,252,437]

EVIDENCE: A meta-analysis of nine systematic reviews of IPLA which included 76 randomized clinical trials (RCTs) and 4,000 patients over a range of surgeries found that IPLA may be of analgesic benefit in the early postoperative period. (The authors note that IPLA may be even more effective for general abdominal and gynecology procedures other than laparoscopic cholecystectomy and that further research in abdominal procedures beyond laparoscopic cholecystectomy is warranted.)[324] The practice of instilling or nebulizing the peritoneum with local anesthetic was first reported in the 1950s but is not widely used in the United States.[324] The peritoneum is highly innervated and is known to respond to surgical injuries with local and systemic immune and inflammatory changes via nociceptors that contribute to visceral pain.[438,439] IPLA has been the subject of numerous RCTs, primarily in laparoscopic cholecystectomy, but also in other open and laparoscopic abdominal and gynecologic operations.[324] A study of patients undergoing abdominal hysterectomy found significant opioid-sparing effects with patient-controlled intraperitoneal infusions of levobupivacaine.[440] A similar study comparing IV lidocaine and IP lidocaine found IP lidocaine reduced morphine requirements slightly,

with significantly lower serum lidocaine levels. The authors conclude that the effects of local anesthetics are "likely to be predominant via local intraperitoneal receptors or anti-inflammatory effects and not via central mechanisms alone."[441] IPLA has been found to reduce postoperative pain and opioid requirements following cesarean section,[250] particularly with peritoneal closure.[442] Further studies are required to determine the efficacy of IPLA. The risk of local anesthetic systemic toxicity is presumed to be lower with IPLA than with IV use, as serum levels of local anesthetic are lower.

DOSING: The authors of one review recommended an IPLA dose of bupivacaine of 2 mg/kg, noting that bupivacaine was the agent used most often in the studies included in their analysis.[247] A review of systemic levels of local anesthetic following IPLA reported no cases of clinical toxicity, though in 2.7% cases patients had systemic local anesthetic levels above or close to a safe threshold; the authors note that the addition of adrenaline to IPLA almost halves systemic levels and prolongs effect.[443]

PREGNANCY AND LACTATION CONSIDERATIONS: See information below.

LIDOCAINE IV INFUSIONS[444,445]

EVIDENCE: IV lidocaine appears to offer better analgesia, results in less nausea and has been shown to reduce the quantity of opioids administered after elective abdominal hysterectomy.[446] IV lidocaine in addition to IV dexmedetomidine significantly improved postoperative pain and enhanced recovery of bowel function following abdominal hysterectomy.[268] Intraoperative IV lidocaine has also been shown to exert a protective cell-mediated immunity in patients undergoing radical hysterectomy.[447] In one review including gynecologic procedures, a perioperative lidocaine infusion (1.5-3 mg/kg/hr following a bolus of 0-1.5 mg/kg) consistently improved postoperative pain scores in patients undergoing open or laparoscopic surgery.[329] Visual analog scale (VAS) pain scores, as well as early (24-hour) and late (up to 72-hour) opioid consumption were decreased. In addition to improving analgesia, a perioperative lidocaine infusion shortened the duration of postoperative ileus by an average of eight hours and decreased the incidence of PONV by 10-20%. Perioperative lidocaine infusions also reduced the length of hospital stay by eight to 24 hours.[329] Another review in a mixed surgery population found the treatment to be most effective in the abdominal surgery population.[328] It is advised that the use of IV lidocaine be strongly considered for patients without epidural catheters.

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

DOSING: Optimal dosing is unknown, but studies suggest IV lidocaine can be given as a bolus (usually 1-2 mg/kg infused over 10 minutes) followed by a continuous infusion of 1-3 mg/kg/hr, continued for 24-72 hours postoperatively. The continuous IV infusion may be used for up to 72 hours if it is effective and no adverse effects are noted.

CONTRAINDICATIONS: Avoid IV lidocaine in patients with unstable coronary disease, a recent myocardial infarction (MI), heart failure, severe electrolyte disturbances, cirrhosis, arrhythmias and seizure disorders.

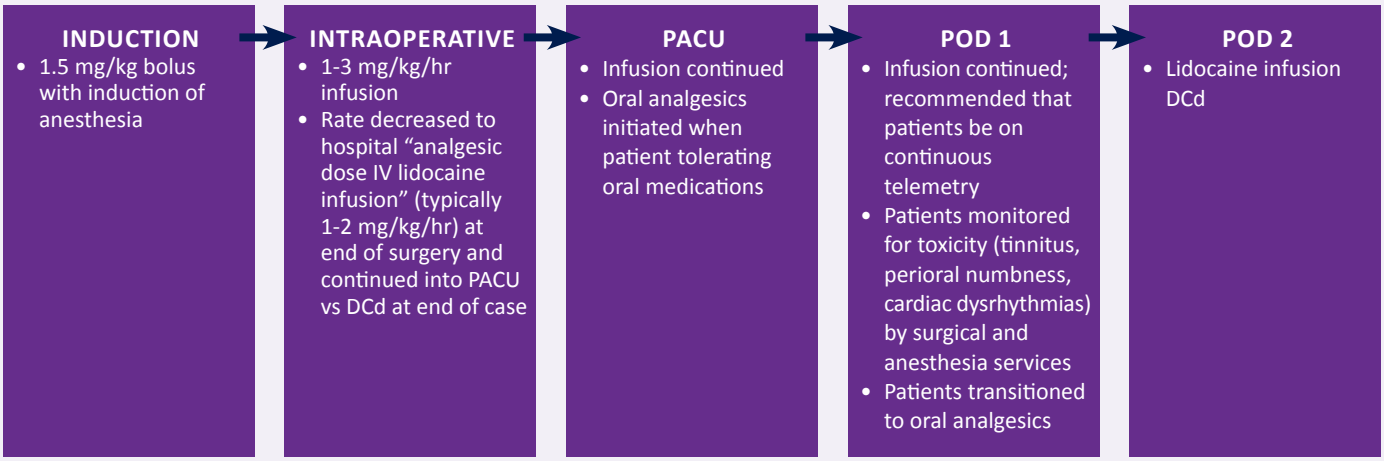
MONITORING: It is recommended that patients should undergo telemetry monitoring.

ADVERSE REACTIONS/CAUTIONS: Local anesthetic systemic toxicity (LAST) is a life-threatening adverse reaction evidenced by circumoral numbness, a metallic taste in the mouth, dizziness, light-headedness and tinnitus. Later signs of toxicity include confusion, slurred speech, blurred vision, myoclonic jerking and seizures. If undetected or untreated, toxicity can progress to coma, respiratory arrest and cardiovascular effects (hypotension, pulse rate <50 or >120, cardiac arrest). If toxicity is suspected, stop the lidocaine and consider a poison center consultation and treatment with lipid emulsion. It is suggested that a lipid rescue kit (i.e., 20% lipid emulsion infusion and appropriate dosing recommendations) be readily available in any practice that uses local anesthetic agents.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Compatible in pregnancy (lidocaine).* Lidocaine rapidly crosses the placenta to the fetus, appearing in the fetal circulation within a few minutes after administration to the mother. While lidocaine has been found to produce CNS depression in the newborn with high serum levels (> 2.5 mcg/mL), cord: maternal serum ratios range between 0.5-0.7 after IV and epidural anesthesia and rarely approach this level if administered appropriately. Both the fetus and newborn are capable of metabolizing lidocaine, and IV, epidural and local infiltration of lidocaine have all been used safely. *Limited human data in breastfeeding—probably compatible.* The potential for harm of the infant from exposure to lidocaine in breast milk is probably very low.

(FIGURE 4)

Perioperative Use of IV Lidocaine



SOURCE: Adapted from Lauren K. Dunn, Marcel E. Durieux; Perioperative Use of Intravenous Lidocaine[329]

LIDOCAINE TOPICAL (TRANSDERMAL PATCHES, GEL AND AEROSOLIZED TOPICALS, EMLA CREAM)

EVIDENCE: While the evidence is somewhat limited and mixed, several small studies support the use of lidocaine transdermal patches for the control of postoperative pain. Studies have found lidocaine transdermal patches effective for patients undergoing gynecologic surgeries.[448] EMLA cream is another topical option backed by limited evidence. One small study in patients undergoing laparoscopic hysterectomy found EMLA, along with trigger-point injections, effective for managing postoperative shoulder pain.[449] EMLA cream is just one of many topical local anesthetic formulations that can be considered. Lidocaine topical agents come in spray, cream, ointment and gel solutions ranging from 1-5%, many of which can be purchased without a prescription. Due to the relatively low risk associated with topical medications, the ability to transition these treatments to the outpatient setting and the availability of over-the-counter products, topical lidocaine transdermal patches and EMLA cream (or similar local anesthetic topicals) can be a reasonable option in most perioperative and discharge analgesic plans. See section above for additional information on dosing and discharge instructions.

PREGNANCY AND LACTATION CONSIDERATIONS: See information above.

LIPOSOMAL BUPIVACAINE[450]

EVIDENCE: Available clinical trial evidence includes investigation of the intraoperative use of liposomal bupivacaine (LB) in both hysterectomy and cesarean delivery with decreased opioid use reported from some of the clinical trials. The benefits of better pain control and/or decreased opioid consumption with LB compared to standard therapy is questionable at this point and additional studies in hysterectomy and cesarean delivery patients are warranted.

In patients undergoing laparoscopic or robotic-assisted hysterectomy, an ultrasound-guided subcostal TAP block with liposomal bupivacaine compared to bupivacaine infiltration was found to reduce opioid pain medication requirements in the first 72 hours and improved patients' quality of recovery.[451] However, it is difficult to attribute the improvement directly to LB versus the difference in technique. A subsequent study in patients undergoing robotic-assisted hysterectomy found that a TAP infiltration with LB compared to plain bupivacaine showed decreased total opioid requirements for the first 72 hours, which is more promising. Another study in laparoscopic hysterectomy patients found that wound infiltration with LB compared to plain bupivacaine did not result in less opioid use or greater measure of functioning.

Literature in the cesarean delivery patient population is also limited. One study found that a LB incisional block at closure resulted in similar postoperative opioid consumption and pain scores.[452] Another small study found that wound infiltration of LB during cesarean delivery reduced postoperative pain scores and opioid consumption.[450] One study directly comparing the use of LB-TAP versus LB incisional infiltration in cesarean delivery found little difference between the two techniques, especially after post-op day zero.[453] Other studies finding a potential decrease in opioid consumption are limited by their retrospective nature.[316,454]

As the literature seems mixed on the clinical and cost benefits of liposomal bupivacaine, especially compared to administration of bupivacaine, it is currently not routinely recommended in these guidelines but may be considered in select cases. Many institutions find it cost-prohibitive to stock liposomal bupivacaine and/or have a very restricted use agreement with surgeons. These guidelines recognize the inherent barriers with this medication and therefore do not routinely recommend its use at this point until further literature can provide more robust support

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

DOSING: Liposomal bupivacaine local infiltration of up to 266 mg (20 mL) injected slowly; max dose = 266 mg; dose based on size of surgical site and individual patient factors. Liposomal bupivacaine should be injected 1-1.5 cm apart with 1-2 mL volumes through a 25 gauge or larger needle to maintain the structural integrity of the liposomes. When injecting surgical incisions, liposomal bupivacaine should be injected above and below fascial planes and into the subcutaneous tissues.

CONTRAINDICATIONS: It is advised that liposomal bupivacaine not be used in obstetrical paracervical block anesthesia, as fetal bradycardia and death have been reported with use of bupivacaine in paracervical block.

MONITORING: It is recommended that liposomal bupivacaine be administered in areas where treatments for neurologic or cardiac toxicity are available (i.e., lipid rescue kit).

ADVERSE REACTIONS/CAUTIONS: LAST is a life-threatening adverse reaction. It is recommended that a lipid rescue kit (i.e., lipid emulsion 20% infusion and appropriate dosing recommendations) be made readily available in any area of practice that utilizes any local anesthetic agent. It is advised that liposomal bupivacaine NOT be directly mixed (in the same syringe or vial) with lidocaine agents; it may be mixed with bupivacaine agents.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *LB is not recommended for use in pregnancy.* Use in obstetrical paracervical block anesthesia is contraindicated; may cause fetal bradycardia and death. *No human data in breastfeeding—potential toxicity.* Bupivacaine is present in breast milk and has the potential for serious adverse reactions in the nursing infant.

SPECIAL CONSIDERATIONS: The main concern of routinely using a relatively high cost-item such as liposomal bupivacaine is the lack of overwhelming literature to support efficacy and cost-avoidance when compared to bupivacaine alone. Liposomal bupivacaine is available as a 266 mg in 20 mL, or 133 mg in 10 mL vial, which cost approximately $175 and $325 per vial, respectively.[455] Compared to plain bupivacaine, this is approximately a 100-fold cost difference in dose. The dose needed is based on size of surgical site and neuroanatomy, volume needed to cover the width and depth of site and patient factors impacting safety of an amide local anesthetic. One suggestion to optimize use of the 10 mL vial of liposomal bupivacaine is volume expansion, which is a procedure that recommends dilution with plain bupivacaine in a one-to-two ratio of bupivacaine equivalence (i.e., a 133 mg/10 mL vial can be mixed with up to 15 mL of 0.5% bupivacaine or 30 mL 0.25% bupivacaine) to provide 250 mg bupivacaine equivalence.[456] The manufacturer of liposomal bupivacaine also describes a volume expansion method in the package insert involving dilution with sterile normal saline of up to 100 mL with a 133 mg/10 mL vial. However, this technique has not been specifically validated in the obstetrician-gynecologist patient population.

LOCAL ANESTHETIC SYSTEMIC TOXICITY (LAST) CAUTION:[457,458]

LAST is a concern when any of the amide anesthetics discussed above are used, and clinicians are encouraged to know suggested dosage limits, cautions and signs of systemic toxicity. For a generally healthy patient, pharmacologic data suggests that the maximum recommended dose of lidocaine is 4.5 mg/kg and bupivacaine is 3 mg/kg, though it is advised that clinicians take into account the varying degree of absorption based on route of administration. It is recommended that caution be exercised when using multiple routes of administration and when using more than one amide anesthetic agent.

LAST manifests in organs of the body that depend upon sodium channels for proper functioning, most critically the cardiovascular and central nervous systems. LAST is a life-threatening adverse reaction evidenced by circumoral numbness, a metallic taste in the mouth, dizziness, light-headedness and tinnitus. Later signs of toxicity include confusion, slurred speech, blurred vision, myoclonic jerking and seizures. If undetected or untreated, toxicity can progress to coma, respiratory arrest and cardiovascular effects (hypotension, pulse rate <50 or >120, cardiac arrest). If toxicity is suspected, stop further administration of the anesthetic and consider a poison center consultation and treatment with lipid emulsion. It is recommended that a lipid rescue kit (i.e., 20% lipid emulsion infusion and appropriate dosing recommendations) be readily available in any practice that uses local anesthetic agents.

LAST may be potentiated in pregnancy and is a potential contributor to maternal mortality. Pregnant patients have lower levels of circulating α1-acid glycoprotein, which results in higher concentrations of unbound local anesthetic. In addition, higher rates of perfusion of injection sites may result in more rapid absorption and higher peak concentration of local anesthetics during pregnancy.[459,460]

Amine Reuptake Inhibitors

AMITRIPTYLINE, DULOXETINE, NORTRIPTYLINE, VENLAFAXINE

EVIDENCE: Though data regarding effectiveness in treating CPP are limited, there is evidence for TCAs and SNRIs being beneficial for treating the neuropathic pain component,[353] if present, and current guidelines recommend consideration in CPP.[72,461,462] A small study in women with CPP showed that amitriptyline, combined with gabapentin, is more effective than amitriptyline alone.[463] TCAs are commonly prescribed in cases of vulvodynia as well. A prospective nonrandomized study demonstrated that women prescribed TCAs had 47% reduction in pain scores.[464] A systematic review of the utility of antidepressants in vulvodynia concluded that there is a need for additional well-controlled trials to identify the characteristics that would predict patients who would benefit from therapy.[465] Anticonvulsants have also been used for vulvodynia with some success, particularly gabapentin.[466,467]

MECHANISM OF ACTION: SNRIs and TCAs increase spinal cord concentrations of serotonin and norepinephrine, which inhibits reuptake by presynaptic neurons.
AGENTS AND DOSING: SNRIs: duloxetine 30 mg PO once daily, may be titrated up to 60 mg PO once daily; venlafaxine 37.5 mg PO once daily, may be titrated up to 225 mg/day in divided doses. TCAs: amitriptyline/nortriptyline 10-25 mg PO once daily (often given at bedtime due to potential for drowsiness); may be titrated up to 100 mg/day in divided doses.
CONTRAINDICATIONS AND CAUTIONS: May increase suicide risk in patients 18-25 years old. Do not use within 14 days of a monoamine oxidase inhibitor (MAOI) due to the risk of serotonin syndrome. Avoid in the elderly (Beers criteria) due to anticholinergic effects.
MONITORING: For TCAs, monitor QTc at baseline and periodically. For SNRIs, monitor for serotonin syndrome. Do not discontinue abruptly if a patient has been taking the drug for an extended period of time; gradual dose reduction is recommended to avoid withdrawal symptoms.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Human data suggests low risk in pregnancy (amitriptyline, nortriptyline)*. Because of the experience with TCAs, some suggest that they be preferred during gestation over other antidepressants. *Human data suggest risk in third trimester (duloxetine, venlafaxine).* Duloxetine causes developmental toxicity in rats and rabbits, though limited human pregnancy experience does not directly suggest an increased risk of birth defects. Selective serotonin reuptake inhibitors (SSRIs) and venlafaxine have been associated with developmental toxicity, including spontaneous abortions, low birth weight, prematurity, neonatal serotonin syndrome, neonatal behavioral syndrome and respiratory distress. *Limited human data in breastfeeding —potential toxicity (amitriptyline, duloxetine, nortriptyline, venlafaxine).*

The U.S. Department of Health and Human Services 2019 Report on Pain Management and Best Practices states, "Overall, the analgesic actions of antidepressants occur even in patients who are not clinically depressed, and their analgesic effect typically occurs sooner and at lower doses than those required for the treatment of depression."[207]

DULOXETINE

EVIDENCE: Although the evidence is inconclusive, one meta-analysis of more than 500 mixed surgical patients found that duloxetine was associated with a significant reduction in pain scores as early as four hours postoperatively and up to 48 hours.[468] In addition, duloxetine was associated with a significant reduction in postoperative opioid use and PONV. Duloxetine 60 mg given prior to and 24 hours after abdominal hysterectomy has also been shown to significantly reduce postoperative opioid consumption.[469] Preoperative duloxetine in combination with dexamethasone IV was found more effective than duloxetine alone for improving pain, reducing the requirements for rescue analgesia, and PONV after laparoscopic gynecologic surgeries. While additional research is warranted to further determine duloxetine's effect on postoperative pain and analgesic use, duloxetine may be considered in the immediate pre- and postoperative periods for appropriate patients undergoing gynecologic surgeries.

DOSING: Duloxetine 60 mg once preoperatively and once 24 hours postoperatively. Typical maintenance dosage for continued use is 60 mg orally once daily.

Anticonvulsants

LAMOTRIGINE, OXCARBAZEPINE, TOPIRAMATE

EVIDENCE: A small open-label, prospective trial of lamotrigine found that it produced statistically significant improvement for generalized vulvodynia.[377] While there is a lack of literature with these agents, similarities in mechanism of action and differing side effect profiles make them reasonable options for patients who have failed other therapies for vulvodynia or chronic pelvic pain.[378]

MECHANISM OF ACTION: Lamotrigine is a triazine derivative which inhibits release of glutamate and inhibits voltage-sensitive sodium channels; oxcarbazepine and topiramate result in blockage of voltage-sensitive sodium channels as well. Topiramate is also thought to enhance GABA activity and inhibit glutamate receptors.

AGENTS AND DOSING: Lamotrigine 25 mg PO once daily, titrated up to 200 mg/day; slow titration is critical to avoid hypersensitivity reactions; decrease dose slowly over several weeks when discontinuing in order to avoid withdrawal symptoms. Oxcarbazepine 150 mg PO twice daily, titrated up to 900 mg PO twice daily. Topiramate 25 mg PO once daily, titrated up to 200 mg/day in divided doses; long-term use requires gradual discontinuation over several weeks to avoid withdrawal.

CONTRAINDICATIONS AND CAUTIONS: Lamotrigine has a black box warning for serious skin rashes, including Stevens-Johnson syndrome.

MONITORING: Hypersensitivity reactions in those taking lamotrigine. Signs of suicidality in those taking oxcarbazepine or lamotrigine.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Compatible in pregnancy if maternal benefit outweighs embryo-fetal risk (lamotrigine).* Lamotrigine and topiramate are not recommended in pregnancy due to reports of increased risk of oral clefts; however, patients with epilepsy may have a higher risk of delivering an infant with a malformation. Limited human data in pregnancy—animal data suggest risk (oxcarbazepine). Oxcarbazepine is embryo and fetal toxic and teratogenic in some animal species. Oxcarbazepine is also not recommended in pregnancy due to risk of congenital malformations. Human and animal data suggest risk in pregnancy (topiramate). The use of topiramate during pregnancy is associated with a two- to three-fold increased risk of malformations, largely due to an increased risk for cleft lip. *Limited human data in breastfeeding—potential toxicity (lamotrigine, topiramate).* Lamotrigine and topiramate cross into breast milk, but the effect on a nursing infant is unknown but may be of concern. *Limited human data in breastfeeding—probably compatible (oxcarbazepine).* Oxcarbazepine crosses into the breast milk but has unknown effects on the nursing infant.

Anxiolytics

BENZODIAZEPINES

EVIDENCE: Multiple studies have shown the preoperative administration of benzodiazepines to be ineffective for reducing postoperative anxiety and pain; some studies show negative effects, including increased time to extubation and recovery.[470-473] However, it may be appropriate to consider a low-dose benzodiazepine for select patients with extreme preoperative anxiety, as significant anxiety may contribute to pain.[474,475]
MECHANISM OF ACTION: Binds to benzodiazepine receptors linked to the GABA-A receptors, enhancing the inhibitory effects of GABA on neuronal excitability.
OPTIONS AND DOSING: Lorazepam 1-2 mg PO/IV once preoperatively and every six hours as needed postoperatively; diazepam 5-10 mg PO/IV once preoperatively and every six hours as needed postoperatively. Midazolam 1-2 mg once preoperatively may be considered, but is typically not recommended for routine use outside of the operative setting.
CONTRAINDICATIONS AND CAUTIONS: Use caution when used concomitantly with other potential CNS depressants. Black box warning: Concomitant use with opioids or other CNS depressants can result in profound sedation, respiratory depression, coma and death.
MONITORING: Monitor for CNS and respiratory depression, and evaluate hepatic function.
PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Human data suggest risk in first and third trimesters (lorazepam). Limited human data in pregnancy—animal data suggest low risk (diazepam, midazolam.)* The effects of benzodiazepines on the human embryo and fetus are controversial. Although a number of studies have reported an association with various types of congenital defects, other studies have not found such associations. Continuous use during gestation has resulted in neonatal withdrawal. *Compatible with breastfeeding—potential toxicity if combined with other CNS depressants (lorazepam, midazolam). Limited human data—potential toxicity (diazepam).*

CLONIDINE

EVIDENCE: Small oral doses of preoperative clonidine have been found to be effective for attenuating preoperative anxiety and reducing postoperative pain and opioid consumption. One study in abdominal hysterectomy patients found clonidine 0.1 mg administered orally as effective as oral melatonin at reducing preoperative anxiety, postoperative pain and postoperative opioid consumption.[475] Another study in abdominal hysterectomy patients found preoperative oral clonidine 0.1 mg to have a clinically relevant anxiolytic effect and to be a potential alternative to other preoperative sedatives.[476] A preoperative oral clonidine 0.2 mg dose has also been found to be as effective as gabapentin in producing preoperative sedation.[477] Overall, it is reasonable to consider a preoperative dose of oral clonidine 0.1 mg to reduce anxiety in patients undergoing gynecologic surgery, and it may also reduce postoperative pain and opioid consumption. (See "Alpha-2 Adrenergic Agonists," above, for more information.)

GABAPENTIN[478]

EVIDENCE: Premedicating highly anxious patients with gabapentin may reduce preoperative anxiety and pain catastrophizing.[479] Premedication with gabapentin (1200 mg) appears to be more effective than hydroxyzine and placebo for the reduction of preoperative anxiety and may lead to greater patient satisfaction.[480] Gabapentin (typically 300-600 mg/dose) is part of many surgical pathways due to its opioid-sparing and pain-attenuating effects. It may be reasonable to give highly anxious patients a higher preoperative dose (e.g., 1200 mg). (See "Gabapentinoids," below, for more information.)

MELATONIN

EVIDENCE: Premedication with melatonin may reduce preoperative anxiety in adult patients and is as effective as standard treatment with midazolam.[301-304] One study in patients undergoing hysterectomy found that preoperative melatonin also reduced morphine requirements, suggesting that administration may also attenuate pain.[481] Additional in vitro, animal and preclinical evidence further suggests that melatonin may have analgesic potential, but further research is needed.[241-244,484] Due to the overwhelming safety profile of melatonin and emerging supportive literature, premedication can be considered for highly anxious patients.

MECHANISM OF ACTION: Binds to the MT1, MT2 and MT3 receptors, which may contribute to the agent's sleep-promoting properties. Its ability to reduce anxiety is thought to be due to its effects on the pineal gland, which impair contextual fear conditioning.[482]

DOSING: 6 mg PO once 60-90 minutes prior to surgery.

Monitoring: Melatonin, particularly as a single dose, is exceedingly safe.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *No human data in pregnancy—animal data suggest moderate risk. Limited human data in breastfeeding—probably compatible (low doses); no human data in breastfeeding—potential toxicity (high doses).*

Beta Blocker

ESMOLOL

EVIDENCE: One study in hysterectomy patients found that beta-blockade with esmolol in anesthesia reduces the intraoperative use of inhalation anesthetic and fentanyl, decreases hemodynamic responses and reduces morphine consumption for the first three postoperative days.[483] A recent meta-analysis of intraoperative esmolol in mixed surgical patients showed that its use reduced intraoperative and postoperative opioid use but had no effect on postoperative pain scores.[273] Another review found that perioperative esmolol reduced postoperative pain intensity, opioid consumption and rates of nausea and vomiting.[330]

MECHANISM OF ACTION: Recent studies suggest that esmolol may have antinociceptive and postoperative opioid-sparing effects, though exact mechanism is unknown; both pharmacokinetic and pharmacodynamic interaction with other anesthetic agents have been proposed.

DOSING: 0.01-0.05 mg/kg/min continuous infusion throughout surgery. May consider an initial bolus of 0.5 mg/kg given over 60 seconds.

CONTRAINDICATIONS AND CAUTIONS: Avoid use in patients with decompensated heart failure, pulmonary hypertension, second- or third-degree atrioventricular block, severe sinus bradycardia and sick sinus syndrome.

MONITORING: Monitor blood pressure and heart rate to assess clinical response.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Compatible in pregnancy—maternal benefit should outweigh embryo-fetal risk.* Cardioselective B1-adrenergic blocking agents are not thought to cause structural anomalies. However, maternal exposure to esmolol has resulted in persistent B-blockade of the fetus and/or newborn. *No human data in breastfeeding—probably compatible.*

Central Prostaglandin Synthesis Inhibitor

ACETAMINOPHEN

EVIDENCE:[484] Acetaminophen in combination with an NSAID has shown efficacy in controlling pain in patients with dysmenorrheic pain.[485] A single oral dose of acetaminophen 1 g has been found to significantly reduce pain in patients with primary dysmenorrhea and was enhanced even further by the addition of caffeine 130 mg.[388] In general caffeine has been found to be a beneficial adjuvant to both acetaminophen and NSAIDs.[486]
MECHANISM OF ACTION: Although not completely understood, it is theorized to be due to an inhibition of central prostaglandin synthesis (specifically COX-2) and an elevation of the pain threshold.
DOSING: Acetaminophen 500-1000 mg by mouth three to four times daily.
CONTRAINDICATIONS AND CAUTIONS: Life-threatening cases of acute hepatic failure leading to liver transplant or death have been linked with acetaminophen use. In most cases of hepatic injury, acetaminophen doses exceeded maximum daily limits and often involved the use of more than one acetaminophen-containing product.
HEPATIC DOSING: For patients with cirrhosis with stable liver function tests (LFTs), reduce the total daily dose to 2 g (expert opinion).[487]
MONITORING: Check LFTs, especially in patients with preexisting liver disease.
DISCHARGE INSTRUCTIONS: Instruct the patient to avoid other over-the-counter products that contain acetaminophen and to limit the total daily dose to less than 4000 mg with short-term and 3000 mg with long-term use.
PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Human data suggest low risk in pregnancy. Compatible with breastfeeding.*

EVIDENCE: Acetaminophen has been demonstrated in clinical trials and systematic reviews to reduce postoperative opioid use by as much as 30% four hours after some surgical procedures.[292-294,488-491] In five randomized controlled trials, acetaminophen significantly lowered pain compared to placebo without increased adverse events. Number needed to treat to achieve pain relief is four.[492] The American Society of Anesthesiologists' 2012 *Practice Guidelines for Acute Pain Management in the Perioperative Setting* recommends including acetaminophen in an around-the-clock, multimodal regimen for the management of postoperative pain (unless contraindicated).[225] ACOG Committee Opinion No. 742 recommends acetaminophen as part of postpartum pain management, particularly following cesarean delivery.[71] Acetaminophen, both alone and in combination with an NSAID, has been found to reduce postoperative analgesic consumption following cesarean delivery.[493,494]
DOSING: Acetaminophen 1000 mg by mouth once prior to surgery. See section above for postoperative dosing recommendations.
SPECIAL CONSIDERATIONS: Acetaminophen has a high bioavailability when administered orally and rectally. It is recommended that IV acetaminophen not be used unless the drug cannot be administered via oral or rectal routes; a 2015 systematic review concluded that there is little evidence for using IV acetaminophen over oral acetaminophen in patients that are able to take medications by mouth perioperatively.[495] While IV acetaminophen may be of utility in surgeries lasting more than six hours, a dose of 1000 mg IV acetaminophen costs approximately $40, compared to pennies for a dose of oral or rectal acetaminophen.
DISCHARGE INSTRUCTIONS: See section above.

Gabapentinoids

GABAPENTIN, PREGABALIN

EVIDENCE: A small study in women with CPP showed that amitriptyline, combined with gabapentin, is more effective than amitriptyline alone.[463] In general, the gabapentinoids are well validated for use in pain with a neuropathic component and should be considered for CPP.[72,496] A small retrospective study compared the use of gabapentin and pregabalin for pain management in urological CPP syndrome and found gabapentin to be more effective than pregabalin.[497] Gabapentin has also been found mildly helpful in treatment of pain associated with vulvodynia.[466,467]

MECHANISM OF ACTION: Structurally related to the neurotransmitter GABA. Thought to inhibit alpha 2-delta subunit of voltage-gated calcium channels, which are believed to decrease the conduction of neuropathic pain sensations.

AGENTS AND DOSING: Gabapentin 100-300 mg by mouth one to three times daily; may titrate up to 3600 mg/day in divided doses. Pregabalin 50-75 mg by mouth one to two times daily; may titrate up to 300 mg/day in divided doses. Pregabalin has better oral bioavailability and a faster onset of action (one hour versus three hours with gabapentin). Dosing recommendations are influenced by renal function.

CONTRAINDICATIONS AND CAUTIONS: Avoid gabapentin in older adults with a history of falls, as it may cause syncope, impaired psychomotor function, dizziness and ataxia. Gabapentin has shown to increase risk of respiratory depression.[498] A number of studies show an increased risk of ORADEs and overdose death when gabapentin and opioids are used concurrently.[499,500] In December 2019 the FDA issued a black box warning for concurrent use of gabapentinoids and opioids or other CNS depressants.[501]

MONITORING: Evaluate serum creatinine levels, watch for sedation.

DISCHARGE: Pregabalin poses a risk of misuse and abuse, requires a DEA waiver (is a schedule V controlled substance) and may be cost prohibitive.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Limited human data in pregnancy—animal data suggest risk.* Some literature suggests concerns of drug-induced developmental toxicity, but this is not consistent across the literature. *Limited human data in breastfeeding—probably compatible (gabapentin)*. Gabapentin is excreted into breast milk, however the effect on the nursing child is unknown. *No human data in breastfeeding—potential toxicity (pregabalin).* Pregabalin crosses into breast milk and may cause side effects in the nursing child.

EVIDENCE: Use of gabapentin in the perioperative period may improve pain outcomes and has been shown to reduce postoperative opioid requirements and promote opioid cessation after surgery.[297,502] Two large meta-analyses demonstrated lowered pain scores and/or opioid requirements with preoperative gabapentin treatment for the first 24 hours following surgery. A meta-analysis specifically in open hysterectomy patients found that gabapentin reduced postoperative opioid consumption and VAS scores.[503] Another large meta-analysis in the same patient population found similar results, along with a reduction in PONV.[504] One study compared preoperative gabapentin to IV ketamine and placebo and found it more effective in reducing postoperative pain scores, as well as preventing chronic pain in the first six postoperative months.[505] One study in patients undergoing laparoscopic hysterectomy also found pretreatment with gabapentin beneficial.[506] While the literature is less compelling with cesarean delivery, perioperative gabapentin has been shown to improve postoperative VAS scores and lead to higher pain control satisfaction. Dosing regimens vary widely among studies included in these meta-analyses, and no concrete determination can be made of optimal gabapentin dosing.[507-509]

A meta-analysis of 43 mixed surgical studies reported a modest reduction in analgesic requirements and postoperative pain with perioperative pregabalin use.[510] An earlier meta-analysis found reductions in postoperative opioid requirements and ORADEs.[511] Preoperative pregabalin has been found effective at reducing postoperative morphine consumption and early postoperative pain in patients undergoing elective cesarean delivery; however maternal side effects were more common compared to placebo.[512] A large meta-analysis found that preoperative use of pregabalin also reduces postoperative pain, total morphine consumption and PONV following hysterectomy.[513] One study in laparoscopic hysterectomy patients found the optimal dose to be 150 mg.[506]

It is suggested that both drugs be considered as part of perioperative multimodal pain management regimen per the American Society of Anesthesiologists 2012 *Practice Guidelines for Acute Pain Management in the Perioperative Setting.*[226]

DOSING: Dosing varies widely for both agents in studies, but typically a starting dose of gabapentin 300-1200 mg preoperatively, followed by 300-600 mg PO one to three times daily. Pregabalin 50-300 mg in the perioperatively, followed by 50-150 mg one to two times daily.[511] Dosing recommendations for both agents are influenced by renal function.

Glucocorticoids

TRIAMCINOLONE

EVIDENCE: Local injection of steroids may be therapeutic in CPP when peripheral nerves are involved.[461]

MECHANISM OF ACTION: Glucocorticoids have analgesic, antiemetic, antipyretic and anti-inflammatory effects.

AGENTS AND DOSING: Triamcinolone 40 mg (usually in combination with a local anesthetic) administered at point of tenderness.

COMPLICATIONS: Risks of glucocorticoid use include gastric irritation, impaired wound healing, impaired glucose homeostasis and sodium retention. However, these are of little to no concern with a one-time local injection.

CONTRAINDICATIONS AND CAUTIONS: Due to the abbreviated nature of glucocorticoid therapy, relative contraindications are of lesser concern; these include adrenal suppression, immunosuppression, myopathy and psychiatric disturbances.

DISCHARGE: Prolonged treatment with glucocorticoids is not recommended due to complications and side effects, and it is suggested that most patients receive only a single dose.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Compatible with pregnancy—maternal benefit should outweigh embryo-fetal risk.* Use in the first trimester has a small absolute risk of oral clefts. However, depending on the indication, the benefit of therapy may outweigh the risk. *No human data in breastfeeding—probably compatible.* The molecular weight of dexamethasone is low enough for passage into breast milk, but effects on the nursing child are unknown.

DEXAMETHASONE[71,514,515]

EVIDENCE: Dexamethasone given perioperatively at doses greater than 0.1 mg/kg may produce a dose-dependent reduction in postoperative pain and an opioid-sparing effect.[516] A single preoperative administration of the drug produces the most consistent pain outcomes. Dexamethasone produces a dose-dependent opioid-sparing effect in the general surgical setting and is particularly effective for reducing pain scores with dynamic movement; these effects have been produced with a single dose of dexamethasone between 10-40 mg with few serious side effects.[515,517,518] Dexamethasone added to local anesthesia in TAP blocks prior to cesarean delivery[519] or abdominal hysterectomy[520] is well validated to prolong duration and improve quality of analgesia. Preoperative IV administration of dexamethasone also reduces pain scores and opioid consumption after cesarean delivery.[514] One study found local infiltration of dexamethasone at the wound site in cesarean delivery improved pain significantly better than did IV dexamethasone, though IV administration is more effective at decreasing PONV.[521] Evidence also supports preoperative IV dexamethasone as part of the baseline analgesic regimen for laparoscopic hysterectomy.[522]

DOSING: Doses of greater than or equal to 0.1 mg/kg are most effective, though minimal additional benefit is seen in doses greater than 0.2 mg/kg. It is recommended that the initial dose be given pre- or perioperatively.

PREGNANCY AND LACTATION CONSIDERATIONS: See above.

Hormonal Therapies

EVIDENCE: A Cochrane review concluded that there is moderate evidence to support progestogen treatment for CPP (e.g., medroxyprogesterone).[523] Dysmenorrhea associated with endometriosis has been found to respond to oral contraceptive therapy, both estrogen and progesterone combinations as well as progesterone alone.[524] As compared to cyclic administration, continuous therapy has been shown to have better pain control.[525] Combinations containing lower doses of ethinyl estradiol (i.e., 20 mcg) as compared to high dose (i.e., 30 mcg) have a lower risk of venous thromboembolism and are currently recommended.[526] GnRH agonists have been found to significantly reduce pelvic pain in patients with endometriosis, however they are approved for continuous use for only up to six months due to concerns for side effects.[527] GnRH antagonists are also an option, providing symptomatic relief and regression of endometriotic implants in patients suffering from endometriosis.[527,528]
MECHANISM OF ACTION: Progesterone-containing contraceptives prevent follicular maturation and ovulation and lead to atrophy of the endometrial tissue. Combined hormonal contraceptives lead to suppression of ovaries and disease activity. GnRH agonists lead to profound hypoestrogenism and amenorrhea.[527] GnRH antagonists cause a lower degree of hypoestrogenism, but without the initial flare and often a better side effect profile.[527]
AGENTS AND DOSING: The list of various hormone replacement agents is extensive, and not all agents are listed here. Depot medroxyprogesterone 150 mg intramuscularly (IM) every 12 weeks for CPP. Medroxyprogesterone 10-100 mg by mouth daily for three to six months for CPP. Norethindrone acetate 2.5-15 mg by mouth daily for up to 12 months for dysmenorrhea and pelvic pain. Leuprolide acetate 3.75 mg IM monthly or 11.25 mg used every three months for pelvic pain in patients with endometriosis. Cetrorelix 0.25 mg subcutaneously once daily for pelvic pain in patients with endometriosis. Levonorgestrel IUS inserted vaginally once, placed for up to five years.
CONTRAINDICATIONS AND CAUTIONS: History of thromboembolic disorders. History of certain cancers. Many of the hormonal therapies suppress ovulation so should not be used in women desiring fertility. GnRH agonists are approved for continuous use for only up to six months due to concerns for side effects secondary to hypoestrogenism like bone loss, vaginal atrophy and dryness, hot flashes and abnormalities in lipid profile.
MONITORING: Weight, glycemic control, lipid profile, abnormal vaginal bleeding.
PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Contraindicated in pregnancy (medroxyprogesterone, leuprolide). Compatible with breastfeeding (medroxyprogesterone, levonorgestrel, norethindrone). Contraindicated with breastfeeding (leuprolide).*

Muscle Relaxants

CYCLOBENZAPRINE, DICYCLOMINE, TIZANIDINE

EVIDENCE: While there is little evidence to support the use of muscle relaxants for analgesia in painful gynecologic disorders, some patients may find benefit. A Cochrane review did not find sufficient evidence to recommend muscle relaxants for myofascial pain in general.[529] One retrospective survey found that dicyclomine combined with an NSAID was well tolerated and effective for patients experiencing primary dysmenorrhea.[389] It is recommended that the appropriate agent be chosen according to its pharmacokinetic profile, side-effect profile, abuse potential and possible interactions.
MECHANISM OF ACTION: Cyclobenzaprine is structurally related to TCAs; acts at the brain stem within the CNS to influence both gamma and alpha motor systems by reducing tonic somatic motor activity. Dicyclomine blocks the action of acetylcholine at parasympathetic sites in smooth muscle and the CNS. Tizanidine is a relatively selective alpha-2 adrenergic agonist with analgesic effects. Also thought to have some activity at the imidazoline receptors, reducing the facilitation of spinal motor neurons. Preferred in patients with spastic disorders due to central activity.
DOSING: Cyclobenzaprine 5-10 mg PO three times daily. Dicyclomine 10-20 mg PO four times daily. Tizanidine: Initial dose = 2 mg orally; may repeat every six to eight hours as needed; increase by 2-4 mg per dose at one- to four-day intervals (max 36 mg/day).
CONTRAINDICATIONS AND CAUTIONS: Do not use cyclobenzaprine in the acute recovery period following an MI or in patients with arrhythmias or congestive heart failure; concomitant use with MAOI within 14 days is contraindicated. Do not use tizanidine with potent CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin). All three agents meet the Beers Criteria.

SPECIAL CONSIDERATIONS: If stopping prolonged use of the medication, baclofen and tizanidine must be discontinued gradually by slowly decreasing the dose to minimize side effects.
MONITORING: Watch for CNS-depressive effects, particularly if combined with other sedating medications.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Limited human data in pregnancy—animal data suggest low risk (cyclobenzaprine). Compatible with pregnancy (dicyclomine). No human data in pregnancy—animal data suggest risk (tizanidine).* Avoid in the first trimester. *No human data in breastfeeding—potential toxicity (cyclobenzaprine, tizanidine). Limited human data in breastfeeding—potential toxicity (dicyclomine).*

NMDA Receptor Antagonists

DEXTROMETHORPHAN

EVIDENCE: A meta-analysis of 14 trials and 848 patients suggests that perioperative dextromethorphan use reduced postoperative opioid consumption at 24-48 hours and pain scores at one, four to six, and 24 hours.[286] It may also attenuate the sensation of acute pain at doses of 30-90 mg, without major side effects, and reduce the amount of analgesics required in 73% of postoperative patients.[300] A study in abdominal hysterectomy patients found both a preoperative 40 mg oral dose and postoperative 40 mg PO three times daily for two days to be analgesic-sparing and attenuate pain.[530] Similar results were found with a single preoperative 150 mg oral dose in patients undergoing abdominal hysterectomy, as well as a preoperative 30 mg oral dose followed by three 30 mg postoperative doses in patients undergoing transabdominal hysterectomy.[287] Patients who receive dextromethorphan 40 mg IM plus ketorolac 60 mg IV prior to laparoscopic-assisted vaginal hysterectomy appear to have better pain relief and a faster recovery of bowel function than those who take either drug alone or other active analgesic agents.[288] A study of an enhanced recovery protocol for cesarean section that included dextromethorphan as a scheduled perioperative medication demonstrated dramatic reductions in opioid requirements and length of stay.[531] Of note, the injectable formulation is not available in the United States, and dextromethorphan can only be administered enterally.
MECHANISM OF ACTION: NMDA receptor antagonist that binds to receptor sites in the spinal cord and CNS, thereby blocking the generation of central acute and chronic pain sensations that arise from peripheral nociceptive stimuli and reducing the amount of analgesics required for pain control.
COMPARED TO KETAMINE: Although ketamine is widely used as a multimodal adjunct worldwide, dextromethorphan does not appear to share the same level of popularity in the United States and is rarely used as an adjunct for postoperative analgesia. The use of dextromethorphan perioperatively may provide similar benefits to preemptive ketamine therapy in a simple oral, intramuscular or IV formulation. Further investigation, particularly a head-to-head randomized trial alongside placebo, may help clarify whether the different NMDA antagonists provide similar levels of relief with a similar incidence of dysphoric or other side effects. Additional research may also explore whether the simultaneous use of more than one NMDA receptor antagonist offers any benefits, as it is unclear whether this approach can result in additive, synergistic or antagonistic effects.[286] In those patients thought to particularly benefit from the use of IV ketamine in the perioperative period, it may be reasonable to transition to an oral NMDA agent, such as dextromethorphan, for continued pain relief. The dosing recommendation made in these guidelines is dextromethorphan 40 mg PO three times daily, which may be reasonable to continue for up to seven days in some patients.[530]
DOSING: 30-90 mg PO administered 30-90 minutes prior to surgery. Doses of 40 mg PO three times daily have also been studied for two days following surgery.
CONTRAINDICATIONS AND CAUTIONS: Avoid in patients taking MAIOs and within 14 days of MAOI use.
MONITORING: May cause dizziness or somnolence. Additional monitoring is not required.
DISCHARGE: Dextromethorphan has not been studied at discharge, but oral formulations may be considered for the continued postoperative treatment of patients who have experienced significant relief from other IV NMDA antagonists (e.g., ketamine).
PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Compatible in pregnancy. Compatible in breastfeeding.*

KETAMINE

EVIDENCE:[276] A large meta-analysis concluded that ketamine reduces pain intensity and analgesic use across multiple different settings and surgeries and likely decreases PONV without increasing side effects.[532] Ketamine IV is associated with lower postoperative opioid requirements and, in most studies, less postoperative pain in opioid-tolerant patients.[335,336,532,533] IV ketamine has also been associated with a lower risk of CPSP.[534,535] While current literature does not support the routine use of IV ketamine for every surgical case, it is reasonable to use the agent to treat patients with preexisting pain, those on COT and those who are predicted to have difficult-to-control postoperative pain (assuming no contraindications exist). In the gynecologic surgery population, evidence is more limited with mixed results. One study in total abdominal hysterectomy patients found that IV ketamine compared to either IV magnesium or placebo resulted in reduced morphine consumption.[263] For use in cesarean delivery, a large meta-analysis found that IV ketamine enhances postoperative analgesia and appears to be safe for both mother and baby, with no effect on Apgar scores.[276]

MECHANISM OF ACTION: Ketamine antagonizes NMDA receptors in the CNS.

DOSING:[364] Typically, the effective IV bolus dose is 0.1-0.5 mg/kg in the surgical setting, followed by an infusion of 0.1-0.5 mg/kg/hr throughout surgery. Dosing is highly related to concomitant anesthetic and analgesic agents, and much higher ketamine doses may be used for sedation while lower doses (typically ≤ 0.3 mg/kg) may avoid psychomimetic side effects. Following surgery, a continuous infusion of 0.1-0.3 mg/kg/hr may be continued based on the provider's discretion and hospital policy. Due to the lack of readily available oral ketamine products, it is reasonable to start considering the discontinuation of an IV ketamine infusion following surgery within 24-48 hours.

CONTRAINDICATIONS AND CAUTIONS: Avoid in patients with seizure disorders, psychosis, poorly controlled hypertension, heart failure, arrhythmia, increased intracranial pressure (e.g., brain lesions, intracranial bleeding), a recent stroke, severe respiratory insufficiency or PTSD. Ketamine can cause dose-dependent sedation.

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

MONITORING: If used in the postoperative period, it is recommended to check vital signs 15, 30 and 60 minutes following the start of infusion (or the administration of a bolus dose), then every four hours for remainder of the infusion. In the case of acute changes in vital signs or intolerable psychomimetic effects, stop ketamine and consider the administration of benzodiazepines to manage psychomimetic effects.

DISCHARGE: Due to the unavailability of ketamine products in the outpatient setting, it is recommended that ketamine be tapered and discontinued prior to discharge. If ketamine is used for more than 48-72 hours, consider a taper prior to discontinuation. Ketamine is a Schedule III drug with potential for abuse.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] *Limited human data in pregnancy—animal data suggest low risk.* Although ketamine anesthesia close to delivery may induce dose-related, transient toxicity in the newborn, these effects are usually avoided with the use of lower maternal doses. There are no reports of malformations in humans or animals attributable to ketamine. *No human data in breastfeeding—probably compatible.*

MAGNESIUM SULFATE

EVIDENCE: A meta-analysis of use of perioperative IV magnesium sulfate in 20 RCTs demonstrated improved postoperative pain both at rest and with movement as well as reduced opioid requirements. The greatest benefit was seen in patients who received magnesium both intraoperatively and postoperatively. None of the included studies reported toxicity.[278] Another meta-analysis found lower postoperative pain scores four to six hours after surgery and reduced opioid use in surgical patients receiving magnesium sulfate.[285,275] Magnesium sulfate can be a useful analgesic adjunct in patients receiving TIVA. It appears to reduce propofol, atracurium and postoperative morphine consumption in gynecologic surgical patients.[284] In a study of gynecologic patients undergoing laparotomy under TIVA, pain scores, analgesic consumption and shivering incidents were lower in the

magnesium group than in the control group, and it was concluded that magnesium sulfate improved the quality of postoperative analgesia during TIVA.[283] Postoperative IV magnesium sulfate infusions may also increase the time to analgesic need and reduce the total consumption of analgesics required after spinal anesthesia.[282] In patients undergoing total abdominal hysterectomy, low-dose intraoperative magnesium infusion reduced postoperative pain morphine consumption and decreased serum beta-endorphin concentration.[279] Another similar study in the same patient population found a single preoperative IV magnesium dose was a safe and effective method to reduce postoperative pain and opioid consumption.[280] In patients undergoing cesarean delivery, literature exists to support the analgesic effect of both IV magnesium as well as adding magnesium to epidural anesthetic. One meta-analysis of neuraxial magnesium in patients undergoing cesarean delivery found a longer duration of neuraxial anesthesia, lower postoperative pain scores at rest and with motion and lower consumption of analgesics.[281] A meta-analysis of IV magnesium in patients undergoing cesarean delivery found improved analgesic outcomes and fewer side effects.[277] Due to the high therapeutic index and relative cost-effectiveness of magnesium, the agent may be a reasonable addition to many pain management regimens and can be routinely recommended in gynecologic surgeries.[333]

MECHANISM OF ACTION: Magnesium is thought to blunt somatic, autonomic and endocrine reflexes provoked by noxious stimuli during surgery.

DOSING: Usual regimens of magnesium sulfate IV include a loading dose of 30-50 mg/kg followed by a maintenance dose of 6-20 mg/kg/hr (continuous IV infusion) until the end of surgery. However, a single bolus of magnesium without a maintenance infusion may also be effective for postoperative analgesia. Magnesium has a relatively large therapeutic index, with concerns of accumulation mostly in the renally impaired population.

CONTRAINDICATIONS: Avoid in patients with heart block and use caution when using prolonged infusions in patients with renal impairment.

MONITORING: Cardiovascular monitoring is recommended to prevent hypotension. Slow administration (>10 minutes) of the loading dose of magnesium sulfate may minimize cardiovascular side effects, such as hypotension and bradycardia. It is recommended that blood pressure be monitored at least every three to five minutes during rapid administration.

DISCHARGE: Magnesium is available in multiple oral formulations, but caution is advised regarding the risk of diarrhea. Oral magnesium supplementation may be appropriate for some patients after discharge.

PREGNANCY AND LACTATION CONSIDERATIONS:[419]
Compatible with pregnancy. Compatible with breastfeeding.

NSAIDs

CELECOXIB, IBUPROFEN, MELOXICAM, NAPROXEN

EVIDENCE: Both non-selective and COX-2-specific NSAIDs have been found effective in treating pain associated with primary dysmenorrhea.[386,536] A 440 mg dose of naproxen was found superior to a 1 g dose of acetaminophen in reducing pain in dysmenorrhea.[537] Of note, one study found ibuprofen in the salt formulation to have a quicker onset of action for pain relief in patients with dysmenorrhea when compared to the conventional form of ibuprofen.[538]

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

OPTIONs: Nonselective agents: Ibuprofen 400-800 mg PO Q 6 hr, naproxen 200-500 mg PO BID. Selective COX-2 inhibitors: Celecoxib 100-200 mg PO BID, meloxicam 7.5-15 mg PO once daily.

DIFFERENT SIDE EFFECT PROFILES: In general, COX-2 selective NSAIDs (celecoxib, meloxicam) have a lower risk of GI and bleeding side effects but a higher risk of cardiac side effects (e.g., MI and stroke).[550,551] Nonselective NSAIDs (naproxen, ibuprofen) have a lower risk of cardiac complications but a higher risk of GI and bleeding side effects. It is suggested that COX-2 selective NSAIDs (e.g., celecoxib) be used for high-risk patients without cardiovascular contraindications.

CONTRAINDICATIONS AND CAUTIONS: NSAIDs can increase the risk of MI and stroke. They are contraindicated in those who have suffered an MI or underwent recent coronary artery bypass graft surgery. These medications can also increase the risk of GI-related complications, including bleeding, ulceration and perforation of the stomach or intestines. This risk is especially pronounced in the elderly (Beers Criteria) and in patients with prior peptic ulcer disease or GI bleeding. Caution is advised for patients on concomitant anticoagulants or antiplatelet agents. Avoiding use in patients with chronic kidney disease, cirrhosis or heart failure is recommended. The risk of renal injury is higher in patients who are elderly, dehydrated or suffer from other comorbidities, including heart failure, diabetes and cirrhosis.

MONITORING: Check serum creatinine levels and discuss any history of GI ulceration prior to initiation.
RECOMMENDED DURATION OF USE: Use the lowest effective dose for the shortest possible duration.
PREGNANCY AND LACTATION CONSIDERATIONS:[419]
Human data suggest risk in the first and third trimesters. Persistent pulmonary hypertension of the newborn may occur if used in the third trimester close to delivery. NSAIDs have been shown to inhibit labor and prolong pregnancy. NSAIDs also have been associated with spontaneous abortion, cardiac defects, oral clefts and gastroschisis. *Compatible with breastfeeding.*

KETOROLAC

EVIDENCE: NSAIDs[71] (e.g., ibuprofen, ketorolac, celecoxib, meloxicam) have been shown to decrease opioid consumption and occurrence of opioid-related side effects.[539] A review of multimodal anesthesia concluded that 600 mg of ibuprofen is as effective as 15 mg of oxycodone hydrochloride.[232] In a meta-analysis of 52 randomized trials of multimodal analgesia with nonopioid analgesics, use of NSAIDs reduced opioid consumption, pain intensity, nausea and vomiting, and sedation compared with morphine alone.[540] A 2005 meta-analysis in a mixed surgical population reported that NSAIDs in conjunction with opioid treatment significantly decreased pain scores and morphine requirements 24 hours postoperatively, with a decrease in morphine consumption at 24 hours of 50% with the COX-2 inhibitor rofecoxib and by 40% with other NSAIDs. The authors found that the addition of NSAIDs or COX-2 inhibitor to a multimodal analgesic regimen also decreased the incidence of PONV, and sedation in both small and large surgeries.[540] Administration of ketorolac in the perioperative period has been found to reduce opioid consumption by 25-45%, thereby reducing opioid-related side effects, including ileus, nausea and vomiting.[541] Specifically in patients undergoing cesarean delivery, preoperative administration of ketorolac leads to reduced shoulder pain and requests for additional intraoperative analgesics.[542] In another study of patients undergoing cesarean delivery under spinal anesthesia, preoperative ketorolac increased time to first analgesic.[543] While IV ketorolac has shown mixed results in laparoscopic hysterectomies,[544] Procedure Specific Postoperative Pain Management (PROSPECT) recommendations still include an NSAID as part of the baseline analgesic regimen for all laparoscopic hysterectomies.[522] When compared to ketorolac in the immediate postoperative period, celecoxib administered prior to robotic hysterectomy and for seven days after surgery was comparable in reducing inpatient pain scores and resulted in less use of prescription opioids for seven days after surgery.[545] The combination of preoperative IV ketorolac and IM dextromethorphan appears to be especially effective in patients undergoing laparoscopic-assisted vaginal hysterectomy, resulting in less pain and opioid consumption, and decreased time to bowel recovery.[288]

AGENTS AND DOSING: Ketorolac 15-30 mg IV Q 6 hours for a max of five days. Dosing for oral agents is found above.
DIFFERENT SIDE EFFECT PROFILES: See section above for additional information. While it is reasonable to recommend the use of a nonselective NSAID (e.g., ketorolac) preoperatively or at induction in most surgical cases where NSAID use is desired, it is advised that the risk of GI side effects and bleeding be considered. It is suggested that COX-2 selective NSAIDs (e.g., celecoxib) be used for high-risk patients without cardiovascular contraindications. In some patients and for some high-risk surgeries in which blood loss is of concern, it may be reasonable to withhold NSAIDs altogether.

SURGERY-SPECIFIC COMPLICATIONS AND CONCERNS:

Postoperative kidney function: Literature on the effect of perioperative NSAID use on postoperative kidney function in patients with normal kidney function is somewhat mixed. NSAIDs appear to have uncertain effects on the risk of postoperative acute kidney injury, but they may slightly increase postoperative serum creatinine levels. It is uncertain whether NSAIDs elevate the need for renal replacement therapy, increase the risk of death or increase lengths of hospital stay.[546] In general, clinical judgment must be used when considering perioperative NSAIDs. Most clinicians agree that NSAIDs be avoided in those with renal dysfunction.

Postoperative bleeding: Literature is somewhat mixed on the association of NSAIDs and the risk of clinical postoperative bleeding, but most experts support the use of NSAIDs for many surgical patients in whom the concern for bleeding is relatively low.[547] The antiplatelet effects of NSAIDs are caused by the reversible inhibition of COX-1. The relationship between the time of NSAID discontinuation and perioperative clinical bleeding is not well-defined, as the elimination half-life of each medication correlates poorly with COX inhibition and platelet aggregation. A long-held belief has been that NSAIDs, particularly ketorolac, increase the risk of surgical bleeding. However, more recently ketorolac was not shown to increase incisional or GI bleeding in patients under 75 years old.[548] Recent meta-analyses in pediatric neurosurgery patients and plastic surgery patients both found no increased risk of postoperative bleeding.[549,550] The risk of operative site bleeding with ketorolac versus parenteral opioids in the perioperative setting appears to be comparable.[551] The risk of GI bleeding and bleeding at the operative site with ketorolac may be dose-related and higher in patients older than 75 years. The risk of GI bleeding (but not postoperative surgical site bleeding) is associated with the duration of administration; it is recommended that ketorolac be given for no more than five days. In contrast, highly selective inhibitors of COX-2 have little or no effect on platelets, making these agents the first-line treatment for patients at high risk of perioperative bleeding; however, such decisions must be balanced with the increased cardiovascular risk associated with COX-2 selective agents. In pregnancy and vaginal delivery, ketorolac is contraindicated due to concern for adversely affecting fetal circulation and inhibition of uterine contractions, thus increasing the risk of uterine hemorrhage.[552]

CONTRAINDICATIONS AND CAUTIONS: See section above.

SPECIAL CONSIDERATIONS: It is suggested that use of ketorolac be limited to five days, given its GI risks, and limited to 15 mg every six hours in patients who are older than 65 years or weigh less than 50 kg as well as in those with moderately elevated serum creatinine.

MONITORING: Check serum creatinine levels and discuss any history of GI ulceration prior to initiation.

RECOMMENDED DURATION OF USE: The American Society of Anesthesiologists *Practice Guidelines for Acute Pain Management in the Perioperative Setting* recommends an around-the-clock NSAID regimen (either COX-2 selective or nonselective) for postoperative pain management unless contraindicated. Use the lowest effective dose for the shortest possible duration.

(TABLE 9)

Risk of Gastric Ulcer Bleeding with NSAIDs

INDIVIDUAL NSAID	ADJUSTED CONDITIONAL RR (95% CI)
LOW	
Celecoxib	1.0 (0.4-2.1)
Ibuprofen	4.1 (3.1-5.3)
Naproxen	7.3 (4.7-11.4)
Indomethacin	9.0 (3.9-20.7)
HIGH	
Ketorolac	14.4 (5.2-39.9)

SOURCE: Lanas A, García-Rodríguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations.[553]

(TABLE 10)

GI Risk Factor Assessment and NSAID Therapy

GI RISK FACTOR ASSESSMENT	TREATMENT
HIGH RISK History of previously complicated ulcer, especially recent ***OR*** more than two risk factors: • Age >65 years • High-dose NSAID therapy • Previous history of uncomplicated ulcers or • Concurrent use of aspirin, corticosteroids or anticoagulants	Alternative therapy or COX-2 inhibitor + PPI
MODERATE RISK • 1 - 2 risk factors	NSAID + PPI
LOW RISK • No risk factors	NSAID alone

SOURCE: American College of Gastroenterology Guidelines, 2009[554]

Other Topical Agents

EVIDENCE: In a small retrospective review, topical amitriptyline-ketamine was found effective for treatment of rectal, genital and perineal pain, and discomfort and may be considered in patients with pelvic pain.[364] Another retrospective of topical gabapentin (2-6%) three times daily resulted in at least a 50% reduction in pain score associated with vulvodynia in 80% of patients.[555] A small retrospective review of women who used 2% amitriptyline and 2% baclofen cream for localized vestibular pain found that over 50% experienced at least a 60% improvement in symptoms.[556] A lidocaine 5% ointment has also shown some success.[557]

OPTIONS: Topical agents are typically compounded by specialty pharmacies and are available in a variety of combinations and vehicles. Combination topical as a 1-2% amitriptyline/0.5-1% ketamine gel or cream, applied one to three times daily. Gabapentin 2-6% ointment, applied three times daily. Lidocaine 5% ointment, applied one to three times daily.

SPECIAL CONSIDERATIONS: Many of the above topical agents are not commercially available and may need to be specially compounded by a pharmacy; this can prove cost-prohibitive for some patients.

PREGNANCY AND LACTATION CONSIDERATIONS:[419] See individual pharmacologic guidance sections for more information. In general, topical agents are not typically systemically absorbed at the same rate as oral or injection administration. However, variable degrees of absorption can lead to similar systemic concerns and should not be discounted when considering therapy.

Nonpharmacologic Interventions

Nonpharmacologic interventions include a wide range of therapies that seek to modify behavior, emotion, cognition and/or sensory inputs.[558,559] Studies of cognitive behavioral interventions, mindfulness, guided imagery, relaxation, hypnosis and intraoperative suggestion have generally been shown to modestly reduce postoperative pain, analgesic use, depression, anxiety and catastrophizing attitudes.[559-561] Such psychological interventions may be delivered in medical and surgical settings by psychologists, nurses or social workers. Delivery of some interventions may be conducted with online, video or audio materials. Studies of online cognitive behavioral interventions have shown small positive effects on pain relief; however, more research is needed in the perioperative patient population.[562] Meta-analyses of music therapy demonstrate decreased anxiety and better sleep in patients with chronic medical illness.[563] Aromatherapy has also demonstrated positive effects on anxiety, pain relief and opioid dose reduction in some nonsurgical populations.[564] Psychosocial interventions studied include educational information access, peer support and online social networking. No rigorous studies have compared different cognitive-behavioral programs, and there is insufficient evidence to recommend one intervention over another. In addition, some degree of patient interest and engagement may be required for certain cognitive-behavioral methods. That said, it is recommended that nonpharmacologic cognitive-behavioral modalities be offered to receptive patients, as such modalities are relatively inexpensive, unlikely to cause harm and may be beneficial.

Physical modalities for the management of pain include TENS, acupuncture and acupressure, massage, and cold and heat therapy.[565] A review of TENS use in surgical patients found an overall reduction in postoperative analgesic use of 25%, though the authors note wide heterogeneity in the TENS methods used.[591] Other studies of TENS therapy have been inconclusive. Evidence supporting the analgesic efficacy of acupuncture and massage is inconclusive, with no high-quality study supporting the use of either modality.[565] Similarly, compelling evidence supporting the efficacy of cold or heat therapy, continuous passive motion, and bracing and immobilization is lacking. While these interventions generally carry very little risk, there is limited evidence to endorse their effectiveness as part of a multimodal approach to perioperative pain management. Patient preference and the cost and availability of these physical interventions must guide their selection and use.

Policy Recommendations

1. **Private and public insurers should provide reimbursement protocols that align with nonopioid pain management initiatives and offer greater flexibility in the design of reimbursement models.[207]**
   a. Pharmacy benefit managers and payers should offer a comprehensive array of nonopioid options in their formularies and be more transparent in communicating the availability of those alternatives to clinicians.
   b. Pharmacy benefit managers and state and federal regulators should ensure that nonopioid analgesics are included on low-cost tiers.
   c. Insurers, hospital systems and government agencies should work together to improve inpatient and outpatient access to nonpharmacologic pain management modalities and evidence-based behavioral health approaches for treating chronic pain and mental health comorbidities (e.g., PTSD, depression, anxiety, mood disorders, SUD).
      i. Insurers and regulators are urged to develop reimbursement policies that support multidisciplinary, multimodal psychological and behavioral health interventions via a range of delivery methods (e.g., in-person, telehealth, internet self-management, mobile applications, group therapy, telephone counseling).

Harm Reduction

c|h|a
Colorado Hospital Association

COLORADO
MEDICAL SOCIETY

COLORADO
CONSORTIUM
for Prescription Drug Abuse Prevention

Harm Reduction

Harm reduction is a set of practical strategies and ideas aimed primarily at mitigating the negative health consequences of SUD, particularly those associated with injection drug use (IDU). The prevalence of IDU has increased in parallel with the epidemic of prescription OUD, as roughly 75% of injection heroin addictions originate with prescription opioid misuse.[566] The harm reduction approach seeks to protect patients from the harms associated with SUD—particularly IDU—until they are ready to seek treatment and recovery. The harm reduction approach views any reduction in negative behaviors and outcomes—including needle sharing, overdose, degree and duration of impairment, absenteeism from work or family duties and health care costs—as a successful intervention.

For all women who inject drugs (WWID), harm reduction aims to prevent infectious diseases, including HIV/AIDS, hepatitis B and C, sepsis, soft-tissue infections and endocarditis; reduce the risk of overdose and other drug-related fatalities; and decrease the negative social consequences of drug use for individuals, families and communities. Past estimates suggest that as many as one in five people who inject drugs (PWID) are infected with HIV, as many as half have chronic hepatitis infections,[567] and many experience soft tissue and invasive bacterial infections. The human and economic costs associated with these consequences of drug use are staggering. Preventing and treating these infections in WWID decreases morbidity and mortality and reduces health care expenditures. Likewise, overdose education and naloxone distribution is a proven strategy for protecting the lives of this highly vulnerable patient population.

While exact data are not available, women comprise a rapidly growing proportion of PWID.[568] In addition to the well-documented risks all PWID face, women are more likely to experience physical and sexual violence, intimate partner violence, poor sexual and reproductive health, challenges in pregnancy and parenting, exacerbation of behavioral health disorders and pervasive stigma and discrimination.[569]

As many as one-third of WWID globally engage in sex work, placing them at increased risk for sexually transmitted infections (STIs), reproductive coercion and gender-based victimization.[569] Threats of violence may compromise a woman's ability to practice safe injection practices and engage in safe sexual behaviors with their intimate partners[570] and during sex work.[571] Women in their early years of IDU experience higher rates of viral and bacterial infection than men.[572-574] Finally, the prevalence of behavioral health disorders in WWID is higher than in men who inject drugs, including mood disorders, anxiety disorders and PTSD.

Gender-specific research is urgently needed to clarify the areas of increased health risk to WWID and to design harm reduction services tailored to women's risks. Many harm reduction efforts are not focused on the specific needs and challenges of WWID, and the lack of specific services for women contributes to their continued vulnerability.

One harm reduction opportunity unique to this population is the way that pregnancy can inspire reduction in use; this coupled with a trusting therapeutic relationship can open the door to ongoing supportive services that can help overcome the corresponding risks associated with the postpartum period.

Harm Reduction continued

Stigma and Bias As Obstacles to Health Care:

Societal expectations that assume women are responsible caregivers often make the stigma that WWID face even greater than that experienced by men. This stigma and its associated legal consequences prompt many women to avoid contact with medical professionals. Many may not present until pain, an advanced state of disease or pregnancy makes the risks of seeking care feel acceptable in exchange for the pain-relieving or life-saving benefit. Some patients will still avoid care, and some may sign out against medical advice or before treatment is complete. While WWID likely care deeply about their health, they often encounter social barriers that discourage them from accessing regular care. Obstetrician-gynecologists who treat these patients with respect and empathy are better able to establish a trusting, therapeutic alliance and may be able to refer patients to addiction treatment and/or to harm reduction agencies. Finally, obstetric-gynecologic patients who inject drugs are more likely to return for care to a practice where all staff treat them with compassion and without judgment. It is imperative that clinicians make the office and hospital settings welcoming and safe for those who seek care. Obstetrician-gynecologists who adopt the practices recommended by the Harm Reduction Action Center (HRAC) may discover a greater sense of competence, efficacy and satisfaction when caring for patients who inject drugs **(TABLE 11)**. Based on years of experience providing care to patients with OUD, HRAC has compiled best practices for providing patient-centered care in collaboration with patients themselves.

(TABLE 11)

Best Practices for the Care of Patients who Inject Drugs

- Respect patients at all times. Patients often overhear health care providers talking about them negatively outside of the room or behind a curtain.
- Avoid negative labels such as “addict,” “druggie,” “junkie” or “drug seeker.”
- Do not assume that patients who inject drugs do not care about their health; such misperceptions are noticed by patients. Fearing negativity and condescension, many patients avoid seeking medical care and attempt to treat their pain and disease with illicit opioids and/or antibiotics.
- Obstetrician-gynecologists are advised to always treat the patient’s pain. Some clinicians reflexively undertreat or minimize pain when they suspect drug-seeking behavior and fear “feeding an addiction.”
- It is recommended that obstetrician-gynecologists provide targeted educational information about risk reduction for patients that use drugs and avoid judgement or shame.
- Obstetrician-gynecologists are advised to ask the patient’s permission to include new or additional team members if they are not part of the primary team.
- Contacting authorities to report illegal substance use is a violation of patient privacy and the Health Insurance Portability and Accountability Act (HIPAA). If law enforcement needs to be contacted (e.g., a mandatory reporting of child abuse), apprise the patient of that plan.
- It is advised that post-discharge planning be conducted with the patient to avoid vague or unrealistic aftercare plans. Specifically, addressing and creating options for nonmedical needs can promote improved adherence to medical treatment.
- Ideally, all members of the medical team—including nurses, medical assistants and administrative staff—should be educated on harm reduction and the compassionate treatment of all patients.

Harm Reduction continued

It is important to recognize the behavioral components of SUD and the frequent comorbidities of pain, anxiety and depression. Successful management of the behavioral health comorbidities, chronic pain, and the social and medical needs of patients with SUD often requires clinicians to aid patients in accessing ongoing care from several clinical specialties. Obstetrician-gynecologists support their patients best with a multidisciplinary team of clinicians including pain specialists where appropriate, behavioral health professionals, social workers, recovery support specialists and harm reduction agencies. Motivational interviewing techniques, CBT, dialectical behavioral therapy and other counseling methods have been shown to be effective for some patients, particularly when paired with appropriate pharmacotherapy and a collaborative harm reduction-minded approach.[575-577] In all cases, compassionate and supportive rather than punitive approaches are indicated, even when patients fail to adhere to treatment plans.

Practice Recommendations

1. **Obstetrician-gynecologists are encouraged to treat WWID and those with other SUDs without judgment. Addiction is a medical condition and not a moral failure, and clinicians are encouraged to meet patients where they are, infusing empathy and respect into the patient/clinician relationship.**
   a. Patients who feel stigmatized, devalued or disrespected are less likely to access regular obstetric and gynecologic care. Clinicians are encouraged to view patients who inject drugs as individuals with unique personal histories, circumstances, challenges and strengths.
   b. Clinicians can help reduce stigma by acknowledging and speaking openly with their patients about the gender norms that add shame and stigma to WWID, especially those who are pregnant.
   c. Patients are best served by being counseled and allowed to seek treatment—or not—at their own pace **(TABLE 12)**. Pressuring or forcing patients into treatment for SUD is ineffective, violates patient autonomy and creates an adversarial rather than therapeutic relationship. Respecting a patient's choices and autonomy is essential to sustaining a viable patient/clinician relationship.
   d. Abstinence is an ideal; in reality, incremental progress may be a more realistic path to treatment and recovery for many patients, and relapse is common even in patients receiving treatment for SUD.
   e. It is recommended that obstetric and gynecologic care and patient education provide specific, useful information on preventing and treating the harms associated with IDU and directly address health concerns rather than lecturing on moral or societal standards.
   f. While treating underlying SUD is a reliable way to improve a patient's overall health, obstetrician-gynecologists are encouraged to provide specific, useful information on preventing and treating the harms associated with IDU as well as acute and preventive care. Though patients with untreated SUD may fail to adhere to treatment plans and preventive recommendations, terminating relationships with such patients may increase harm to the patient and is not advised.

(TABLE 12)

Counseling Patients Who Inject Drugs

DO	DON'T
• Use respectful language when discussing patients' substance use. • Assess patients' readiness to change. • Respect patients' decisions regarding treatment. • Encourage patients to be honest with providers about any substance use. • Make information available that is specific to the needs of patients.	• 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. It is recommended that obstetrician-gynecologists educate their patients with OUD and those who inject drugs in overdose recognition, prevention and the use of naloxone. Patients may be counseled and educated as follows:

a. Avoid using alone.
   i. Overdoses that occur when patients use opioids alone often result in death.
   ii. Inject in the presence of others. Colorado's Good Samaritan laws protect individuals who call 911 to report an overdose, exempting both them and the overdose victim from arrest and prosecution for minor drug charges.

b. Always carry naloxone.
   i. Naloxone is safe and effective both in and out of the hospital. Since 1996, the opioid antagonist has reversed more than 26,000 overdoses.[578]
   ii. Numerous studies over the past 20 years have confirmed that laypeople can administer naloxone out of hospital with therapeutic success.[578-582]

c. If injecting heroin or fentanyl, first inject a small dose to assess potency.
   i. Variations in drug potency are common, especially with the common practice of cutting or substituting heroin with fentanyl or carfentanil.
   ii. When trying a new product, encourage patients to use a small dose (i.e., test shot) to gauge its potency.

d. Do not mix opioids with alcohol, benzodiazepines, barbiturates or other sedating drugs.

e. Do not go back to using the same dose after a period of abstinence, which often occurs after hospitalization, incarceration or a period of sobriety.

f. Consider using fentanyl test strips. Many harm reduction organizations distribute fentanyl test strips. For people without access to harm reduction services, test strips are available for purchase online.

Fentanyl Testing Strips

The inadvertent use of fentanyl and other highly potent synthetic fentanyl analogues by people who use drugs has contributed to the rise in overdose death seen in the United States and Colorado. Heroin and counterfeit prescription opioids are often mixed with fentanyl and highly potent fentanyl analogues, increasing risk of overdose. As of June 2020, much of the supply of heroin and counterfeit opioid pills sold in Colorado contains fentanyl. Fentanyl or fentanyl analogues may also be added to stimulants, and clinicians may advise their patients who use methamphetamine and other stimulants of the risk of overdose associated with fentanyl exposure, and the utility and availability of fentanyl test strips.

Many people who use drugs report concern regarding the uncertain presence of fentanyl in their drugs, and even more indicate a desire to know if their drugs contain fentanyl.[583] Some harm reduction agencies advocate for the off-label use of fentanyl testing strips (e.g., BTNX fentanyl testing strips) by people who use drugs prior to use. The majority of people who use drugs report that knowing if their drugs contained fentanyl would alter their behavior associated with drug use (e.g., using test shots or seeking out non-fentanyl containing drugs instead).

BTNX fentanyl testing strips were found to have the highest sensitivity and specificity as well as the lowest detection threshold of fentanyl testing technologies evaluated, with a sensitivity between 96-100% and specificity between 90-98%.[583] BTNX can detect other fentanyl analogues including carfentanil, acetylfentanyl, butyrylfentanyl, 3-methylfentanyl, ocfentanil and sufentanil.[584]

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

At this time, CO's CURE leadership and participating organizations take no position on the use of fentanyl testing strips.

3. **Obstetrician-gynecologists are advised to provide naloxone to patients at elevated risk of overdose; if naloxone cannot be directly given, it is recommended that patients receive a prescription and be informed about the over-the-counter availability of naloxone in most Colorado pharmacies.**
    a. Clinicians and health care systems are urged to consider directly dispensing naloxone from the clinic or hospital to any patient with known or suspected IDU. The risk is widespread; the antidote is not. Despite their effectiveness, take-home naloxone programs are present in fewer than 10% of U.S. counties.[585]
    b. PWID have contact with other people at risk of overdose. While patients will rarely rescue themselves with naloxone, they can often use the drug to rescue others who may have inadvertently overdosed.
    c. It is recommended that family members and friends be counseled on recognizing and responding to the signs of overdose and administering naloxone.
    d. Obstetrician-gynecologists are encouraged to work with hospitals that do not have overdose education and naloxone distribution programs to establish take-home naloxone programs to provide the antidote to high-risk patients at discharge.

(TABLE 13)

Criteria for Dispensing or Prescribing Naloxone to High-Risk Patients

It is recommended that naloxone be dispensed directly to patients who:

- Received care for opioid intoxication or overdose
- Have suspected SUD or nonmedical opioid use
- Are prescribed more than 50 mg MME per day
- Are receiving an opioid prescription for pain AND
  - A prescription for methadone or buprenorphine
  - A history of acute or chronic pulmonary disease
  - A history of renal dysfunction, hepatic disease or cardiac comorbidities
  - Known or suspected excessive alcohol use or dependence
  - Concurrent use of benzodiazepines or other sedatives
  - Known or suspected poorly controlled depression
- Are taking opioids but have unreliable access to emergency medical services
- Were recently released from incarceration
- Have resumed opioid use after a period of abstinence

4. **It is advised that obstetrician-gynecologists 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 in most pharmacies.**
   a. Colorado law protects physicians who prescribe naloxone. The State-Specific Policy Summaries Third-Party Naloxone Bill (Colorado SB 13-014) removes the following:
      i. Civil liability for prescribers
      ii. Criminal liability for prescribers
      iii. Civil liability for layperson administration
      iv. Criminal liability for layperson administration
   b. Colorado Good Samaritan Law (Colorado Revised Statutes [C.R.S.] § 18-1-711 and HB 16-1390)
      i. Samaritan acting in good faith
      ii. No arrest or prosecution for possession
      iii. No arrest or prosecution for paraphernalia and protection from other crimes
   c. Standing Orders for Naloxone (Colorado SB 15-053): Any medical professional with prescriptive authority can write a standing order for naloxone that can be dispensed by other designated individuals (such as pharmacists and harm reduction organizations).
      i. With these standing orders, pharmacists and harm reduction organizations can now provide naloxone to those who might benefit from it the most, including:
         1. A family member, friend or other person in a position to assist a person at risk of overdose
         2. An employee or volunteer of a harm reduction organization
         3. A first responder
         4. An individual at risk of overdose
   d. A list of pharmacies that participate in Colorado's standing-order naloxone protocols can be found at www.stoptheclockcolorado.org.
   e. Additional resources: https://www.colorado.gov/cdphe/naloxoneorders

5. **Obstetrician-gynecologists are encouraged to be familiar with the types of psychoactive substances available for legal and illegal purchase and the routes of administration for those substances so that they can effectively communicate with patients about drug use and potentially unsafe practices.**
   a. It is recommended that clinicians be aware of natural and synthetic substances that patients with SUD may use either to experience their psychoactive effects or in an attempt to self-treat SUD. It is advised that clinicians inquire about use of herbal or "natural" substances their patients use in addition to more commonly misused substances.
   b. In some cases, patients will attempt to self-treat OUD with nonmedical substances, including cannabinoids and kratom.
      i. Despite a now-discredited epidemiologic study and popular misconception, no evidence supports the use of cannabinoids as a treatment for OUD. (**SEE APPENDIX IV, CANNABINOIDS AND PAIN**, for details.)
      ii. Kratom is a legally available substance derived from the leaves of the Southeast Asian kratom tree. Kratom contains mitragynine and 7-α-hydroxymitragynine, compounds that bind opioid receptors, producing sedation, euphoria and analgesia. Mitragynine also has stimulant effects. There are reports of patients with OUD or AUD using kratom as an herbal alternative to pharmacotherapy to reduce craving and ameliorate withdrawal symptoms. No evidence supports the efficacy or safety of kratom for addiction treatment. Kratom is known to cause neonatal opioid withdrawal syndrome (NOWS) and to be lethal in overdose. Its use during pregnancy is strongly discouraged.[586]
   c. Obstetrician-gynecologists are advised to be aware that novel synthetic psychoactive substances with no medical use are in near-constant development. These substances are distributed and sold primarily on the internet, and though many are dangerous, they remain legal until health authorities and drug enforcement agencies identify them and hinder their sale.
   d. For a comprehensive description of drugs used for nonmedical purposes, see the National Institute on Drug Abuse's Commonly Used Drugs, published June 2020.

6. **Counseling patients on safer injection practices may prevent complications of IDU, including viral, soft-tissue and invasive bacterial infections and vein sclerosis. Preventing the acquisition and transmission of infectious diseases improves patient health, reduces health care costs and decreases risk for clinicians.**
   a. The vast majority of medical professionals are unfamiliar with drug injection methods and are ill prepared to discuss safeguards with PWID. Clinicians may wish to familiarize themselves with the steps to injecting drugs, including what common and/or unsafe practices are associated with each step and how to mitigate risk.
   b. Most IV drug users learn from their peers and often learn unsafe and dangerous habits. It is important for clinicians to be able to speak with patients knowledgeably about IDU, identify unsafe practices and educate patients on safer injection practices.
   c. The average PWID injects three to five times per day. The risk of transmission of viruses is highest when drug paraphernalia is shared between multiple users within a short period of time. Pathogens can be spread easily via injection equipment (e.g., needles, syringes, cookers [spoons], injection water and cottons).
      i. Hepatitis B and C are particularly virulent and can survive between one and three weeks outside of the body.
      ii. Although HIV can survive only minutes outside the body, it can live for days to weeks inside hollow-bore needles.
   d. Obstetrician-gynecologists are encouraged to be knowledgeable about how to prevent vein sclerosis and preserve veins in PWID. Ideally, patients would be counseled on safe practices prior to discharge.
   e. *Getting Off Right:* A Safety Manual for Injection Drug Users is a good resource for safe injection practices written by and for PWID, with medical advisors involved. https://harmreduction.org/wp-content/uploads/2011/12/getting-off-right.pdf

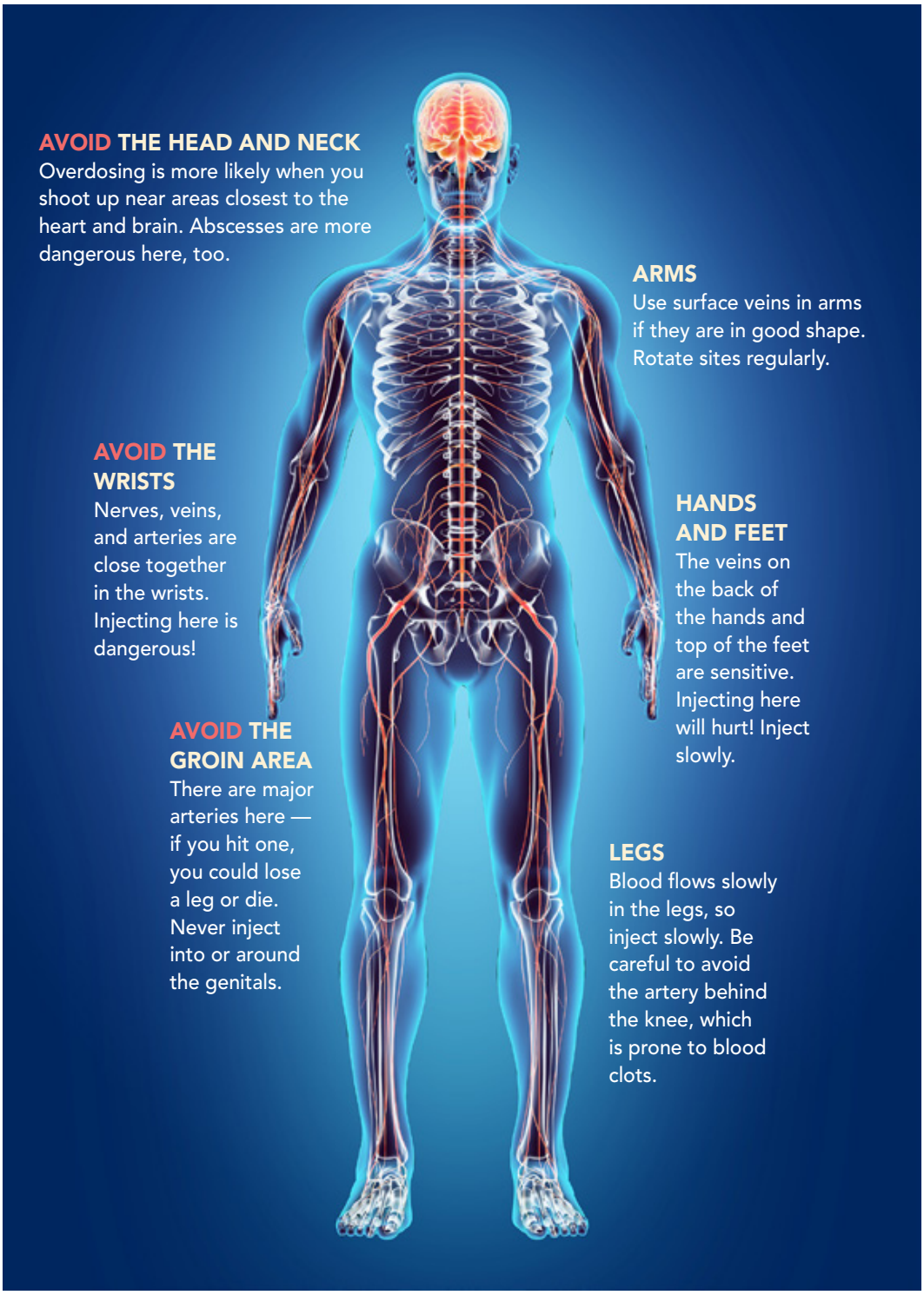
Harm Reduction continued

Patients who inject drugs are best served by being counseled to:

a. Never share equipment. Viral infections can be prevented by never sharing injection materials, including needles, syringes, cookers and cottons. If sterile materials for injection are unavailable, use an alternate route of administration.
b. Practice good hygiene. Use of sterile equipment and good injection hygiene reduces the risk of skin and soft tissue infections and of invasive bacterial infections like endocarditis.
   i. Always wash hands before injecting.
   ii. Use alcohol pads to sterilize skin prior to injection.
   iii. Never lick needles prior to injection.
c. Use new, sterile equipment.
   i. Reusing equipment increases the risk of bacterial contamination.
   ii. Patients can obtain new equipment for free through local syringe access programs (formerly referred to as needle exchange programs).
   iii. If such resources are unavailable, patients can purchase needles, syringes and alcohol pads at a pharmacy.
d. Use sterile water to prepare the product.
   i. Many infections stem from unsafe water supplies; some users report using river water, toilet water or saliva to dissolve product into an injectable form.
   ii. Bottled water is NOT sterile. Used water bottles are contaminated and pose a high risk of infection.
   iii. Optimally, patients should use single-use containers of sterile water.
   iv. If single-use containers of sterile water are unavailable, it is recommended that water be sterilized by heating it at rolling boil for 10 minutes and allowing it to cool.
e. Avoid injection into subcutaneous or muscle tissue rather than into a vein ("skin popping" or "muscling.") These practices predispose patients to abscesses and soft-tissue infections.
f. In order to prevent vein sclerosis and destruction:
   i. Use the smallest (highest gauge) needle possible; rotate injection sites, starting distally.
   ii. Drink water to remain well hydrated.
   iii. Use citric acid if an acidic solution is required to dissolve product (use of lime, lemon or orange juice is discouraged, as these are more sclerotic and carry a higher risk of infection).
   iv. Avoid using the jugular, femoral or pedal veins, which can further increase the risk of infection **(FIGURE 5)**.
g. Refer to *Getting Off Right: A Safety Manual for Injection Drug Users*, a resource for people who inject drugs, written collaboratively by medical professionals and PWID. https://harmreduction.org/wp-content/uploads/2011/12/getting-off-right.pdf

(FIGURE 5)

Safer Injecting for Patients



SOURCE: 2017 Colorado ACEP Opioid Prescribing & Treatment Guidelines

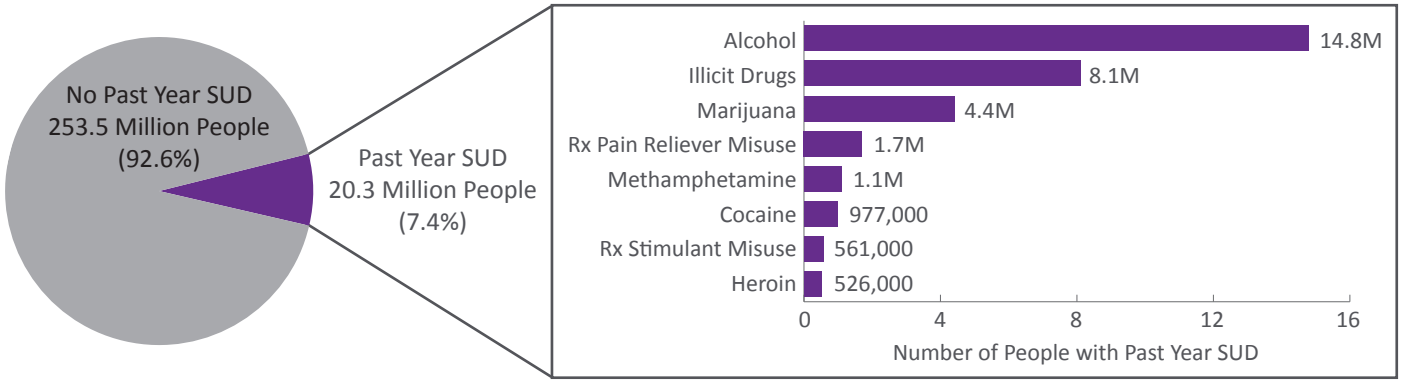
Harm Reduction continued

7. **It is recommended that patients who inject drugs be offered testing, prevention and treatment as indicated for hepatitis C virus (HCV), hepatitis B virus (HBV) and HIV.**
   a. Patients who inject drugs are among the most vulnerable patients obstetrician-gynecologists encounter. They frequently avoid contact with medical professionals and thus hospitalization or an acute care visit may pose a rare opportunity for testing, prevention and/or treatment of bloodborne pathogens in this patient population.
   b. Injection drug use is an important risk factor for HCV infection.
      i. Hepatitis C is a curable disease when treated with medications such as sofosbuvir or combination medications such as ledipasvir/sofosbuvir.
      ii. The U.S. Preventive Services Task Force recommends screening all adults at least once for HCV; obstetrician-gynecologists are encouraged to test any patient who inject drugs for HCV regularly. It is advised that pregnant patients be screened for HCV infection.
   c. HBV is a preventable disease. Clinicians are encouraged to test patients who inject drugs for HBV and/or offer a first HBV vaccination to patients who inject drugs, with directions to complete their course either at their obstetrician-gynecologist clinic or at a harm reduction or syringe access program.
   d. It is advised that HIV testing, treatment and prevention be offered to all patients who inject drugs and patients who test positive for HIV be treated or referred to care. Obstetrician-gynecologists are advised to make patients aware of the availability of medications for both postexposure and preexposure prophylaxis for HIV infection. According to the CDC, when taken daily preexposure prophylaxis with emtricitabine/tenofovir reduces the risk of getting HIV by at least 74% in patients who inject drugs.[587]

8. **Clinicians are encouraged to refer patients who inject drugs to local syringe access programs, where they can obtain sterile injection materials and support services, including counseling, social support, HIV/hepatitis testing and treatment referrals.**
   a. Syringe access programs are cost-effective for reducing HIV transmission and prevalence.[588]
   b. The additional resources these centers often provide (e.g., sterile water, cooking units and cleaning solutions) also help reduce the harms associated with IDU.
   c. WHO suggests a "compelling case that needle and syringe programs substantially and cost effectively reduce the spread of HIV among PWIDs and do so without evidence of exacerbating injecting drug use at either the individual or societal level."[589] In 2000 the AMA adopted a position strongly supporting the efficacy of these programs when combined with addiction counseling.[590]
   d. An online list of local syringe access and harm reduction programs can be found through the North American Syringe Exchange Network. **SEE APPENDIX VIII, MAP AND LIST OF SYRINGE ACCESS PROGRAMS IN COLORADO**.

(FIGURE 6)

Substance Use Disorder Among U.S. Residents Aged 12 and Older in 2018



Rx = prescription

NOTE: The estimated numbers of people with substance use disorders are not mutually exclusive because people could have use disorders for more than one substance.

SOURCE: SAMHSA[591]

9. **Obstetrician-gynecologists are encouraged to offer an addiction medicine consultation or referral to every patient who injects drugs. Evaluation and care from other behavioral health clinicians, social workers and recovery support specialists as available and indicated may also be of benefit to patients.**
   a. Treatment of underlying SUD is the most direct way to assure a patient's long-term health. Patients with injection SUD frequently have multiple medical, obstetric-gynecologic and/or behavioral health comorbidities. In addition, WWID may benefit from assistance with housing, employment, education, legal matters, transportation and/or childcare. Obstetrician-gynecologists are encouraged to ensure that a multidisciplinary team capable of meeting these diverse social and health care needs is in place to care for their patients who inject drugs.
   b. It is recommended that hospitalized patients be offered inpatient consultation with an addiction medicine specialist when available. Addiction medicine clinicians are trained to evaluate the treatment needs of patients with SUD, initiate MAT if appropriate, educate patients about MAT and other SUD treatment, and aid transition to treatment once a patient leaves the hospital.
   c. Obstetrician-gynecologists are encouraged to assure patients who do not wish to receive addiction care that assistance will be available when and if the patient desires treatment and support. It is recommended that patients be provided with verbal, written and/or online information to aid in future efforts to access care.

Harm Reduction continued

10. WWID should be capable of safely injecting themselves. Clinicians are advised to caution patients against relying on others, particularly intimate partners, for injection, as this increases risk of exploitation and deprives women of control over their health and safety.

a. WWID are frequently initiated into IDU by male sexual partners and are more likely to be injected by others (including sexual partners) than to inject themselves.[592,593]

b. Women who are dependent on their sexual partner for drugs or injecting practices have limited control over their own injecting behavior and less capacity to protect themselves from infection and overdose.[594] Traditional gender roles can reinforce power imbalances within male-female injection partnerships,[595,596] encouraging the female partner to play a passive role in the shared injection experience. When women and men inject together, men are more likely to control the purchase, preparation and administration of illicit substances, and women are more likely to be injected with previously used equipment.[597]

c. Women whose injection partner is also a sexual partner have an elevated risk of HCV infection compared with women and men without concurrent sexual and injection relationships.[572,598]

d. One-third of PWID report an injection-related injury or disease (such as abscess, cellulitis, sepsis and endocarditis).[599,600] Rates in women may be higher, possibly because women tend to have less superficial veins, which complicates venous access.[601] The fact that women are more likely to be injected by others contributes to the risk of injection-related injury and disease.

11. Clinicians are encouraged to screen patients universally for intimate partner violence (IPV).[602] Women who inject drugs are at elevated risk for intimate-partner violence and other sources of physical, sexual or emotional abuse.

a. In the United States, approximately 4.8 million women are physically assaulted each year by an intimate partner.[603] An estimated one-third of women in the United States will be victims of physical or sexual violence and/or stalking by an intimate partner in their lifetime.[604] IPV is most prevalent among those of reproductive age and contributes to medical, behavioral health, obstetric and gynecologic harms, unintended pregnancy and STIs.[605]

b. Women who inject drugs are more likely to be victims of IPV than those who do not inject drugs. One study found that 70% of women using community harm reduction services in Europe had experienced IPV in the previous year.

c. IPV is a risk factor for HIV infection in WWID.[606] Conversely, women with HIV experience IPV at much higher rates than women without HIV.[607]

d. One study found a correlation between missed obstetrician-gynecologist appointments and IPV, and a strong correlation between IPV and depression.[607]

e. When caring for patients who are experiencing IPV, obstetrician-gynecologists are advised to document patient statements, provide referrals and/or resources, offer validation and support, assess the patient's immediate safety and develop a safety plan with the patient.

f. See **APPENDIX IX**, Intimate Partner Violence Screening Questions, for guidance from ACOG in discussing IPV with patients.

(TABLE 14)

ACOG Recommendations for IPV Screening[608]

- Screen for IPV in a private and safe setting with the patient alone and not with the patient's partner, friends, family or caregiver present.
- Self-administered written or computerized assessments are as effective as verbal screening in identifying IPV.
- Use professional language interpreters and not someone associated with the patient.
- At the beginning of the assessment, offer a framing statement to show that screening is done universally and not because IPV is suspected. Also, inform patients of the confidentiality of the discussion and exactly what state law mandates that a physician must disclose.
- Incorporate screening for IPV into the routine medical history by integrating questions into intake forms so that all patients are screened whether or not abuse is suspected.
- Establish and maintain relationships with community resources for women affected by IPV.
- Keep printed take-home resource materials such as safety procedures, hotline numbers and referral information in privately accessible areas such as restrooms and examination rooms. Posters and other educational materials displayed in the office also can be helpful.
- Ensure that staff receives training about IPV and that training is regularly offered.

12. Obstetrician-gynecologists are advised to ask their patients who inject drugs if they are engaged in sex work and provide them with or direct them to resources to reduce harm and risks associated with sex work.

a. As many as one-third of WWID are estimated to engage in sex work.[609]
b. The risk of violence from clients and law enforcement officials is substantial, particularly for women who are street-based sex workers.[610-612]
c. WWID are frequently excluded from brothels and thus may participate in higher-risk street-based sex work.[613]
d. WWID who engage in sex work may experience financial pressures to support their own drug use and, in some cases, that of their partners. Decision-making regarding potentially hazardous practices during sex work may be impaired by intoxication or withdrawal.[569]

13. Obstetrician-gynecologists are advised to offer reproductive health services and counseling including contraception and STI screening to all WWID.

a. Incidence of IDU in women is highest during late adolescence and young adulthood—life stages where women are most in need of sexual and reproductive health care.
b. Given the underutilization of obstetric-gynecologic care by WWID, many WWID will have unmet needs for contraception and untreated STIs.
c. Female-controlled contraception is advised to reduce the high rates of unintended pregnancy, reproductive coercion and abortion in WWID.[614,615]
d. Opioid use and poor nutrition may contribute to amenorrhea in WWID, and WWID may not realize they are pregnant until later in pregnancy, increasing the likelihood of poor outcomes for both women and their infants.[613]

Harm Reduction continued

14. **During the postpartum period, when rates of overdose are elevated, obstetrician-gynecologists are positioned and encouraged to ensure that patients with OUD or polysubstance use receive medical and behavioral health care, social and harm reduction support, overdose education and naloxone in order to minimize the risk of overdose.**
    a. The postpartum period is one of both decreased resources and increased stressors for many women.
    b. The normal challenges of parenting a newborn may be increased by the shame and stigma associated with having an infant with NOWS.
    c. Normal postpartum physiologic changes may make optimal opioid agonist dosing challenging.
    d. Rates of discontinuation of MAT are high in the postpartum period. One study found a discontinuation rate of 56% by six months following delivery.[616] Obstetrician-gynecologists are urged to enlist all available resources to aid patients in continuing treatment.
    e. High rates of behavioral health comorbidities and instability in housing likely contribute to overdose risk and further underscore the need for comprehensive support of patients with OUD in the months and years following delivery.

15. **Obstetrician-gynecologists are encouraged to seek out educational opportunities to better understand the care of pregnant WWID.**
    a. Resources available to clinicians include:
        i. ACOG
            1. Maternal Transitions in Care for the Mother-Infant Dyad Affected by Opioid Use Disorder
            2. Caring for Pregnant and Breastfeeding Women with Opioid Use Disorder
            3. Alcohol abuse and other substance use disorders: ethical issues in obstetric and gynecologic practice. Committee Opinion No. 633. American College of Obstetricians and Gynecologists.
            4. Opioid use and opioid use disorder in pregnancy. Committee Opinion No. 711. American College of Obstetricians and Gynecologists.
            5. Substance abuse reporting and pregnancy: the role of the obstetrician–gynecologist. Committee Opinion No. 473. American College of Obstetricians and Gynecologists.
        ii. American Society of Addiction Medicine (ASAM)
            1. The ASAM National Practice Guideline 2020 Focused Update Webinar – Pregnant Women.

Harm Reduction continued

Policy Recommendations

1. **Harm reduction agencies and community programs that provide resources for PWID should be made readily accessible to all Coloradans in need and up-to-date referral information be made available to clinicians. Local, state and federal agencies should establish and fund harm reduction programs and organizations that address the needs of women who inject drugs.**
    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.
    c. These programs, many of which also provide basic medical and social services to this high-risk population, should be well funded and expanded beyond their current levels.
    d. Ideally these programs, many of which also provide basic medical and social services to this high-risk population, would be well funded and expanded beyond their current levels.
    e. WWID may be more likely to seek out harm reduction providers that provide women-only environments, offer childcare and support the safety of women engaged in sex work and women who are victims of violence. Harm reduction agencies that employ women, particularly women in recovery, may be more accessible to WWID.
2. **When local programs are unavailable for WWID, hospitals should consider establishing their own programs to provide services such as safe syringe exchange.**
    a. Colorado SB 19-227 allows for syringe access out of hospitals and EDs, limiting liability. Hospitals should consider partnering with their local health departments and state and federal authorities to establish programs that foster harm reduction. Ideally, such initiatives would be funded by national or state governments, nonprofit organizations or grants to make this service cost effective for participating hospitals.
    b. This recommendation is especially applicable to rural communities, which are particularly vulnerable to communicable disease outbreaks and are unlikely to have local syringe access programs.
    c. Clinicians in these environments have an opportunity to offer or refer WWID to additional medical care, harm reduction and/or social services as needed.

Treatment of Opioid Use Disorder

c|h|a
Colorado Hospital Association

COLORADO
MEDICAL SOCIETY

COLORADO
CONSORTIUM
for Prescription Drug Abuse Prevention

Treatment of Opioid Use Disorder

While men are more likely to be diagnosed with OUD, rates of opioid misuse and addiction, heroin use and opioid overdose have risen more rapidly for women—particularly those of reproductive age—than for men.[566,617,618] Between 1999 and 2015, the rate of death from prescription opioid overdose in women increased 471%, while the rate of increase was 281% in men.[101] Heroin deaths increased at twice the rate in women than in men, and rates of death from synthetic opioids increased 850% over this time period. Though roughly one-third of opioid overdose deaths now occur in women,[619] the opioid epidemic has in many respects had a disproportionate effect on women, as the children born to women with OUD are themselves impacted. Patterns and features of addiction and the barriers to treatment for women vary from those seen in men, and better understanding these differences is essential to preventing, diagnosing and treating opioid misuse and addiction. The term "telescoping" describes the quicker onset of physical dependence and addiction after first use of a substance seen in women when compared to men. Differences in metabolic rate, percentage body fat and hormonal changes likely contribute to telescoping. Research suggests further that women may experience stronger cravings for a number of substances, including opioids, than do men, which may impede recovery.[620-625]

Women are more likely than men to be the present or past victim of physical, sexual or emotional abuse, a factor that substantially increases vulnerability to substance misuse and addiction.[626] Obstetrician-gynecologists are advised to be vigilant in universally screening patients for current trauma, particularly IPV. Research finds that a history of emotional abuse and distress is a risk factor for nonmedical use of prescription opioids in women but not in men.[625] Women experiencing IPV or sexual abuse are at increased risk of harm from substance use.[627] Women with OUD in particular have been shown to experience increased rates of IPV.

A history of trauma increases risk for SUD. Accumulating research into the effect of adverse childhood experiences (ACEs) clearly demonstrates a correlation between ACEs and the probability of developing SUD in adulthood. ACEs are potentially traumatic events experienced between birth and age 17; they can be roughly categorized into direct emotional, physical and/or sexual abuse of the child and experiences of dysfunction in the home. Women are more likely to have experienced ACEs than men, likely in part because rates of sexual abuse are higher in girls and women than in males of all ages. Indeed, women are four times more likely to have a history of childhood sexual abuse than men, and a history of sexual abuse is strongly correlated with presence of SUD.[628] In Colorado, 17.4% of women report a history of four or more ACEs, while only 12.1% of men did.[629] Across a range of studies,[630] rates of a history of trauma in patients who misuse substances range from 55-99% in women, while the rate in the general population is roughly 15%.[631] One study of patients seeking treatment for OUD found that more than 80% had experienced at least one traumatic childhood event and two-thirds had witnessed violence.[632] Individuals who report five or more ACEs have triple the likelihood of misusing prescription opioids and five times the risk of engaging in IDU. Age of initiation of drug use, ongoing IDU and lifetime number of overdoses all correlate closely with an individual's reported number of ACEs.[633] It is worth noting that higher number of ACEs correlates also with greater likelihood of being prescribed opioids for chronic pain in adulthood, which for many patients initiates OUD.[634-637] Moreover, the number of ACEs correlates strongly not only with addiction, but also with non-addiction behavioral health morbidity and with increased risk of STIs, obstetric and neonatal morbidity, teen pregnancy, involvement in sex trafficking and increased rates of cancer, diabetes, cardiovascular disease and suicide.[638-642]

There is no neat causality between addiction, trauma, behavioral health, and obstetric and gynecologic morbidity; rather, personal and intergenerational experiences of trauma, addiction and poor health fuel one another and constrain patients' ability to lead healthy lives. Perhaps the most effective measure to reduce rates of SUD in women would be to reduce adverse and traumatic experiences of all types. This would require addressing poverty, sexism, racism and income inequality; making high-quality education, social supports and health care available to all families and children; and strengthening the social safety nets that prevent child abuse and neglect. While primary prevention of trauma through such sweeping structural societal changes are clearly outside the scope of obstetric-gynecologic practice, obstetrician-gynecologists can advocate for laws and policies that reduce social and economic inequity. The impact of trauma and

ACEs—and the intergenerational perpetuation of trauma and addiction—can be mitigated through several evidence-based measures. Obstetrician-gynecologist practices are encouraged to adopt trauma-informed care practices to improve care and support resilience **(TABLE 15)**. Obstetrician-gynecologists may screen patients and families for evidence of ongoing or past trauma and provide access to effective care, support and treatment for children and families in which ACEs have already occurred in order to strengthen family members' resilience and disrupt the cycle of adversity. The CDC offers guidance to clinicians on use of screening tools and interventions with proven efficacy in *Preventing Adverse Childhood Experiences (ACEs): Leveraging the Best Available Evidence.* The health and well-being of pregnant and parenting patients and that of their infants are inextricably tied. Health care systems thataddress the needs of the maternal-infant dyad with co-located services and/or multidisciplinary medical, behavioral health and social support specialty clinicians who closely collaborate will provide optimal care to these vulnerable patients.

(TABLE 15)

The Substance Abuse and Mental Health Services Administration (SAMHSA) Six Principles of a Trauma-Informed Approach

1. **Safety** – Ensure the physical and emotional safety of clients and staff.
2. **Trustworthiness and Transparency** – Provide clear information about what the client may expect in the program, ensure consistency in practice and maintain boundaries.
3. **Peer Support** – Provide peer support from persons with lived experiences of trauma to establish safety and hope and build trust.
4. **Collaboration and Mutuality** – Maximize collaboration and the sharing of power with consumers to level the differences between staff and clients.
5. **Empowerment, Voice and Control** – Empower clients and staff to have a voice, share in decision-making and goal-setting to cultivate self-advocacy.
6. **Cultural, Historical and Gender Issues** – Move past cultural stereotypes and biases, offer gender- and culturally responsive services and recognize and address historical trauma.

SOURCE: Trauma-Informed Care Walkthrough Project Report—Data and Findings

Of the estimated 2.1 million people in the United States with OUD, fewer than 20% receive evidence-based pharmacologic treatment.[84] Women with SUD are less likely to access care than are men with SUD.[643] When they do enter treatment, women require more extensive medical, behavioral health and crisis management services than men.[644] The consequences of this treatment gap for OUD 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. OUD is a chronic, relapsing medical illness. Like patients with other chronic illnesses, patients diagnosed with OUD need ongoing comprehensive, evidence-based care.

Obstetrician-gynecologists are well positioned to help people with untreated OUD access care. Physicians working today have an opportunity to radically change the care of this patient population by screening patients universally and linking patients to evidence-based care in a non-stigmatizing, compassionate manner. Obstetrician-gynecologists can ensure that patients receiving opioid agonist therapy are maintained on their medication throughout the perioperative and peripartum periods. Finally, they can establish practices and protocols so that appropriate referrals are made for any patient who wants to initiate MAT. By adopting these approaches, obstetrician-gynecologists can make an enormous contribution to improving the lives of people with OUD.

Opioid Use Disorder in Pregnancy

Rates of OUD in pregnant patients have increased dramatically in parallel with rates in the general population over the past two decades.[645] Administrative data from more than 1.4 million pregnant women in the United States from 2009 to 2014 found that 0.57% were diagnosed with OUD during pregnancy or at delivery.[646] Intravenous use of opioids in pregnancy is associated with a range of adverse outcomes for newborns, including increased risk of intrauterine growth restriction, abruptio placentae, fetal demise, preterm labor, transmission of HIV and intrauterine passage of meconium.[647] Pregnant patients with OUD are at elevated risk for overdose and high-risk behaviors that can expose themselves and their fetuses to negative health and social outcomes.

Pregnancy and the postpartum period represent a time of both vulnerability and opportunity for pregnant patients with untreated OUD, who may be exceptionally motivated to access care. Pharmacologic treatment for OUD in pregnant and postpartum women has been demonstrated to significantly improve obstetric, neonatal and SUD outcomes.[648-650] As for all individuals, treatment of OUD saves and improves lives for pregnant and parenting patients. Pregnant patients with untreated OUD frequently receive limited or no prenatal care and may present only in late stages of pregnancy or in labor. The stigma surrounding OUD leads some patients to avoid care, while past negative experiences with the health care system make other patients wary of medical providers.

Compounding the barriers to treatment that pregnant patients with OUD face, confusion and misinformation surrounding treatment of pregnant patients with OUD results in reluctance or refusal to provide essential care. Despite the endorsement of MAT in pregnancy by ACOG, the American Academy of Addiction Psychiatry, ASAM and the American Academy of Pediatrics (AAP), state-to-state variation in laws and regulations adds to the lack of clarity regarding screening, treatment and reporting of substance use in pregnancy and the postpartum period.[651] Some women (in some states appropriately) fear prosecution or incarceration for either illicit substance use or exposing their fetus to illicit substances in utero.[652] Others may fear loss of custody of their children and some lack the resources to access care.[653] Treatment of OUD improves outcomes for pregnant patients and their infants, and obstetrician-gynecologists are encouraged to support laws and policies that view OUD in pregnancy as a medical rather than a legal matter.

Obstetrician-gynecologists are uniquely positioned to provide care that is tailored to the needs of their patients with OUD. A multidisciplinary team of obstetricians, neonatologists, addiction medicine specialists, social workers and other behavioral health clinicians is often needed to meet the complex needs of pregnant and parenting patients with OUD. It is essential that individuals with OUD be screened and treated for other behavioral health conditions. The most frequent behavioral health comorbidities among pregnant women with OUD are nonopioid SUD (78.2%), followed by tobacco use disorder (74.9%), generalized anxiety disorder (38.0%), major depressive disorder (36.9%), cannabis use disorder (28.3%) and cocaine use disorder (27.4%).[646] A literature review confirms that as many as one-third of women with OUD have behavioral health comorbidities; this figure may be an underestimate, as behavioral health symptoms and diagnoses are often underreported by pregnant women out of fear of stigma and involvement of child protective services.[654] Expert opinion broadly holds that integrated treatment for both OUD and nonaddictive behavioral health conditions increases treatment retention and improves outcomes.[654]

The impact of OUD on maternal morbidity and mortality in Colorado has been substantial, with rates of overdose death increasing in the state in parallel with rates of overdose death in the general population. From 2004 to 2012, overdose was the leading cause of maternal mortality, and opioids were the substance most likely implicated in maternal overdose death.[655] Most recent data for Colorado finds that substance use, including opioid use, is now the second leading cause of maternal mortality.[656] Research finds that the risk of overdose is greater in the first trimester and in the first year postpartum.[657] Among possible factors contributing to this increased postpartum risk of overdose is the relative paucity of resources available to patients in the postpartum period; the hormonal changes that complicate MAT dosing; increased rates of depression and anxiety in the

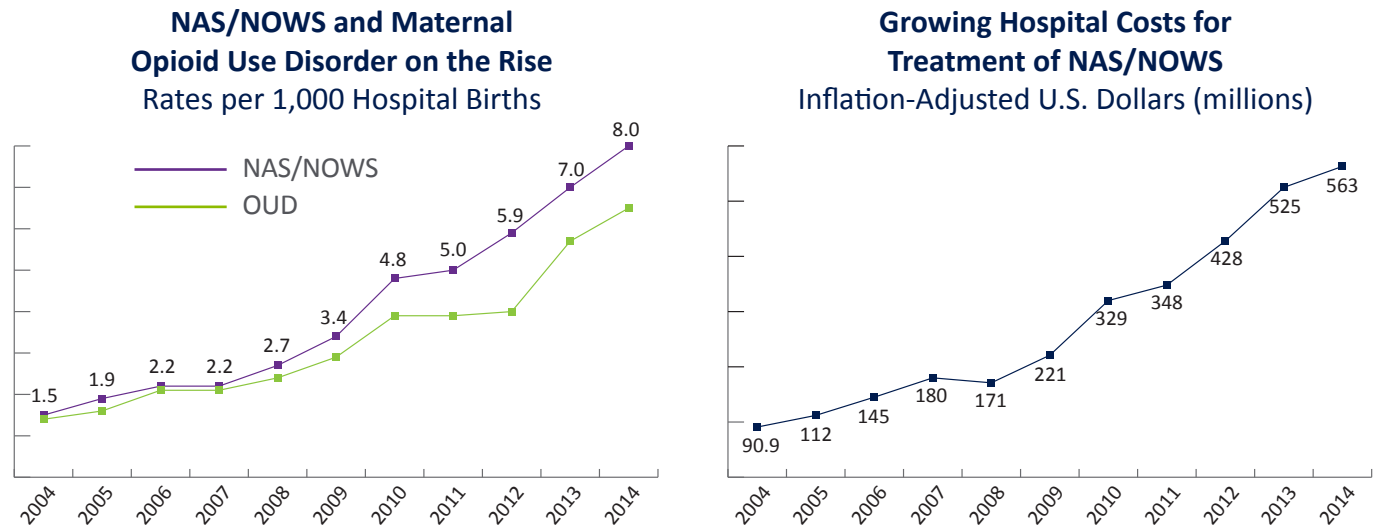
postpartum period; the emotional and financial strains and sleep deprivation common in the postpartum period; and the shame and stigma that may be intensified by watching a newborn experience NOWS. Rates of MAT discontinuation after pregnancy vary regionally, with one systematic review of MAT discontinuation finding a discontinuation rate of 56% at six months postpartum.[616] The association of MAT discontinuation and relapse in OUD is well established, and it is advised that efforts be made to retain women in treatment in the postpartum period.

Neonatal Opioid Withdrawal Syndrome (NOWS)

Opioid use during pregnancy is increasing correspondingly with the national rates of opioid use, though due to lack of standardization in provider and hospital coding practices it is difficult to ascertain precisely the rate of NOWS in Colorado or the United States.[658,659] The latest national data indicates that the incidence of NOWS increased 433% from 2004 to 2014, from 1.5 to 8.0 diagnoses per 1,000 live hospital births.[660] This data equates to one infant being born with NOWS every 15 minutes in the United States in 2014, or about 32,000 infants that year with associated hospital costs estimated at $563 million[659] in 2014 **(FIGURE 7)**. The cost of treatment for newborns with NOWS is five times that of newborns without NOWS.[661]

(FIGURE 7)

Maternal Opioid Use and Neonatal Opioid Withdrawal Syndrome



SOURCE: Public Health Surveillance of Prenatal Opioid Exposure in Mothers and Infants[662]

Treatment of Opioid Use Disorder continued

Observational studies find that 40-80% of infants born to individuals who inject heroin have NOWS. Given that buprenorphine and methadone are opioids, it is unsurprising that infants of patients receiving pharmacotherapy for OUD also exhibit signs and symptoms of NOWS; indeed, observational studies find 13-94% of infants born to patients receiving methadone and 22-67% of infants born to patients receiving buprenorphine experience NOWS. The wide variation in observed rates of NOWS is likely a result of differences in diagnostic criteria and lack of standard treatment of NOWS.

The somewhat lower incidence of severe NOWS seen in neonates of patients receiving buprenorphine or methadone compared with those with untreated OUD may be due to several factors. MAT medications generally provide more consistent concentrations of opioid than do shorter-acting opioids like immediate-release oxycodone, fentanyl or heroin used inconsistently. Patients receiving MAT have lower rates of polysubstance use, which may reduce likelihood of NOWS.[663,664] In addition, patients treated with MAT have lower serum cortisol levels compared with those who are untreated.[665] OUD treatment programs, particularly those specifically designed to treat pregnant women, often provide or facilitate referral to behavioral health care, social supports and parenting education not accessible to women whose OUD is untreated.[111] Finally, women receiving MAT are far more likely to be able to safely breastfeed than those using heroin. Breastfeeding reduces NOWS severity both through transfer of opioid through breastmilk and via physical comforting.[666]

The most recent data on the rate of infants born with NOWS in Colorado shows that the rate of NOWS increased from 2.6 cases per 1,000 hospital births in 2011 to 5.4 cases per 1,000 hospital births in 2018. Experts suspect that the rate in Colorado may be significantly higher. The Colorado Hospitals Substance Exposed Newborns (CHoSEN) quality improvement collaborative finds that among participating Colorado hospitals, the prevalence of prenatal opioid exposure in newborns is nearly double that of publicly reported estimates.[667]

Practice Recommendations

1. **Obstetrician-gynecologists are encouraged to universally screen patients for SUD.**
   a. While some patients present with a clear diagnosis of OUD, patients with OUD may not disclose their disease out of fear of judgment or being reported to child protective services. Others may not be fully aware that they have OUD. A patient of any socioeconomic status, race or ethnicity can develop OUD. Screening only patients who appear high risk due to factors such as poor prenatal care adherence or prior adverse pregnancy outcome leads to missed cases as well as stigma and stereotyping.[668]
   b. Obstetrician-gynecologists and their staff should consider using the Screening, Brief Intervention and Referral to Treatment (SBIRT) protocol to identify and address risk for substance misuse and SUD in all patients.[669]
      i. Use of SBIRT protocols allows risk stratification of women based on their patterns of substance use. It is recommended that low-risk women receive brief counseling, moderate-risk women receive a brief intervention (based on principles of motivational interviewing) and those who are assessed to be high risk referred to specialty care.
      ii. Properly documented SBIRT is reimbursed by private and public insurers. Current billing codes for SBIRT are available at https://www.samhsa.gov/sbirt/coding-reimbursement. The screening component of an SBIRT protocol can be any validated screening instrument. Colorado SBIRT (http://www.sbirtcolorado.org/) is an excellent resource for clinicians.

Health care practitioners who conduct screening and brief intervention (SBIRT) interviews are advised to:

1. Ask the patient for permission to discuss substance use.
2. Elicit the patient's own description of their substance use.
3. Explain any connection between the patient's use and their health complaint (if applicable).
4. Share information about risks of use, including low-risk alcohol limits (if applicable).
5. Ask the patient what they think of the information just provided.
6. Ask the patient about their perceived pros and cons of their use, then summarize what the patient said.
7. Ask what the patient wants to change about their use.
8. Gauge patient's readiness and confidence to reach their goal. If using a Readiness Ruler, ask "Why not a lower number?"
9. If the patient sounds ready, ask them to identify a plan of change.
10. Affirm patient's readiness to change and affirm their plan.
11. Plan to schedule follow-up.

c. Motivational interviewing seeks to elucidate discrepancies between a patient's current behavior and their future goals, a process that may be facilitated in pregnant patients with SUD, the vast majority of whom want to have a healthy infant. Core techniques employed in motivational interviewing include:
   i. A nonjudgmental, empathic manner
   ii. Use of open-ended questions
   iii. Establishing trust and rapport
   iv. Identifying and supporting the patient's own motivations to reduce or eliminate hazardous substance use
   v. Providing accurate, non-shaming education and feedback to the patient regarding their substance use
   vi. Accepting patient resistance without anger, frustration or termination of treatment

Obstetric Considerations

a. Pregnancy is often the first time women are diagnosed with OUD and offered treatment. ACOG,[670] AMA, AAP and CDC support universal use of Screening, Brief Intervention and Referral to Treatment (SBIRT) for pregnant patients.[648] The WHO recommends that clinicians ask all pregnant women about past and present use of alcohol and nonmedical use of licit and illicit substances.[668] Use of SBIRT protocols has demonstrated efficacy in reducing alcohol and tobacco use.[671-678] While further research is warranted, preliminary evidence suggests that SBIRT provides benefit to women with SUD of illegal substances.
b. It is advised that screening be performed at the first prenatal visit and repeated at a minimum of every trimester for women with a history of hazardous substance use or SUD. (ACOG 711).[648]
    i. While evidence suggests use of standardized screening instruments increase the rate of detection of SUD in pregnant women, one study found that fewer than half of obstetricians report universal use of screening tools.[679-682] Screening at every visit may be appropriate, as women who are initially unwilling to disclose substance misuse may share more information with clinicians after a therapeutic alliance is established.[683]
    ii. It is suggested that routine screening also rely on validated screening tools such as questionnaires including TWEAK, T-ACE, 4Ps, NIDA Quick Screen, AUDIT-C and CRAFFT (for women 26 years or younger). For screening pregnant patients, the use of an instrument validated in prenatal settings is advised. (The commonly used CAGE-AID [cut down, annoyed by criticism, guilty about drinking, eye-opener, adapted to include drugs] was not developed for use in pregnant patients).[682]
    iii. Obstetrician-gynecologists are advised to inform patients that these questions are asked of all pregnant patients to ensure optimal care. A compassionate, non-stigmatizing approach that emphasizes the clinician's dedication to the patient's health and well-being is essential to developing patient trust and a therapeutic alliance.
    iv. Given the high rates of tobacco and alcohol use in pregnant women with OUD, obstetrician-gynecologists are encouraged to counsel their patients on the specific, permanent harms associated with the use of alcohol and tobacco in pregnancy **(FIGURE 8)**. It is advised that patients be screened for use of these substances, offered a brief intervention or treated/referred to treatment as appropriate.
c. It is recommended that written educational material about substance use in pregnancy be provided to all pregnant patients, as screening may fail to identify patients who do not accurately report hazardous substance use or SUD.

(FIGURE 8)

Maternal Opioid Use and Neonatal Opioid Withdrawal Syndrome

Past month, 2015 – 2017, 15 – 44

Special analysis of the 2017 NSDUH Report.

+ Difference between this estimate and the 2017 estimate is statistically significant at the .05 level

SOURCE: SAMHSA: The National Survey on Drug Use and Health: 2018[684]

2. **A non-stigmatizing, medically accurate, empathic approach to the patient with SUD is most effective in eliciting an accurate substance use history and building a therapeutic patient-clinician alliance.**
   a. Research shows that effective communication with patients decreases patient anxiety, improves prenatal care attendance and leads to better clinical outcomes.[685-687] A quarter or more of hospitalized patients with untreated OUD will leave against medical advice due to craving, withdrawal, fear of stigma, or mistreatment or social pressures.[688]
   b. Techniques to build a therapeutic alliance with patients include:[689]
      i. Sitting at a similar height with the patient
      ii. Establishing eye contact
      iii. Allowing patients to speak without interruption
      iv. Using nonverbal cues (nodding) to indicate active listening
      v. Paraphrasing the patient's words to demonstrate understanding and attentive listening
      vi. Asking open-ended questions
      vii. Normalizing the patient's experience (e.g., "many patients with OUD…")

c. Obstetrician-gynecologists are encouraged to use straightforward language when delivering education or information, and to confirm that their patients understand the ideas and recommendations being offered.
d. Obstetrician-gynecologists are advised to screen, interview and counsel patients without friends or family members present in order to facilitate open communication.
e. For patients whose routine initial screen suggests possible substance misuse, hazardous use or SUD, clinicians are encouraged to conduct more specific screening as appropriate and to obtain a complete substance use history including:
    i. Age and circumstances of first substance use.
    ii. Substances and routes of administration for all substances used in the past.
    iii. History of medical complications, tolerance, withdrawal and/or overdose.
    iv. Current substances used, with frequency, doses and routes of administration.
    v. Use of legal substances, such as tobacco, alcohol and/or cannabinoids.
    vi. Past experience with treatment and/or recovery.
f. The principles and techniques of motivational interviewing can be powerful tools when engaging with patients with SUD. More information about motivational interviewing can be accessed at https://www.integration.samhsa.gov/clinical-practice/motivational-interviewing

3. It is recommended that obstetrician-gynecologists be well versed in diagnosing patients with OUD.
a. OUD and SUD more generally are poorly understood by many medical professionals. The gap in knowledge begins in medical school, where SUD is inadequately taught. 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 have a formal addiction curriculum.[692]
b. OUD is defined by the DSM-5 and replaces "opioid abuse" and "opioid dependence" as a diagnostic entity.

Obstetric Considerations

1. Patients may fear that clinicians will report substance use in pregnancy to legal or child protective authorities.[690] A series of interviews with pregnant women with SUD found that 73% of the 30 women interviewed reported fear of legal consequences of their substance use and/or loss of child custody, and half of those avoided prenatal care because of these concerns.[691]
2. Clinicians and systems of care that fail to address the fear, shame and ambivalence pregnant women with OUD may experience can fail to adequately care for these vulnerable patients.
3. Colorado does not hold pregnant women with substance-exposed newborns criminally liable.
4. Obstetrician-gynecologists are advised to inquire about their patients' prior experiences with SUD treatment in pregnancy. Information about previous successful (or unsuccessful) treatments, the outcome of prior pregnancies and the current status of previous children may inform treatment decisions.
5. Obstetrician-gynecologists are advised to inquire about the involvement of the patient's partner and family in the current pregnancy. It is recommended that clinicians determine whether or not the patient's partner or other close contacts involved in the pregnancy have untreated SUD. Every effort should be made to help the patient's partner access addiction care. If the patient is amenable, appointments with involved family members and/or the patient's partner may aid in supporting pregnant patients with OUD.

(TABLE 16)

Summarized DSM-5 Diagnostic Categories and Criteria for OUD

Category	Criteria
Impaired control	• Opioids used in larger amounts or for longer than intended • Unsuccessful efforts or desire to cut back or control opioid use • Excessive amount of time spent obtaining, using, or recovering from opioids • Craving to use opioids
Social impairment	• Failure to fulfill major role obligations at work, school, or home as a result of recurrent opioid use • Persistent or recurrent social or interpersonal problems that are exacerbated by opioids or continued use of opioids despite these problems • Reduced or given up important social, occupational or recreational activities because of opioid use
Risky use	• Opioid use in physically hazardous situations • Continued opioid use despite knowledge of persistent physical or psychological problem that is likely caused by opioid use
Pharmacological properties	• Tolerance as demonstrated by increased amounts of opioids needed to achieve desired 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

In order to be diagnosed with OUD, a patient must meet two of the 11 criteria within a 12-month period. Two to three criteria indicates mild OUD, four to five criteria indicates moderate OUD and six to seven indicates severe OUD.

SOURCE: SAMHSA: The National Survey on Drug Use and Health: 2018[684]

c. 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.
d. OUD is a problematic pattern of opioid use leading to clinically significant impairment or distress. Persons who are prescribed opioids often exhibit pharmacological dependence but would not necessarily be considered to have OUD; the presence of tolerance and/or withdrawal in a person receiving opioids under medical supervision for treatment of chronic pain or addiction does not meet criteria for a symptom of OUD.
e. It is important for obstetrician-gynecologists to understand the limitations of toxicology screening used in the care of patients with OUD.
    i. Biological tests cannot diagnose SUD, gauge its severity or provide information about frequency or duration of drug use or routes of administration.
    ii. False positive rates for urine toxicology may be as high as 15%. It is advised that confirmatory testing be performed on any positive screen.
    iii. A urine screening should be performed only with the patient's consent. Patients should be informed of the risks and benefits of urine screening. It is advisable to ask if the patient expects positive results in a nonjudgmental manner in order to facilitate communication.

Urine Toxicology and OUD

1. Many opioids are not detected by routine urine toxicology by immunoassay. Use of synthetic opioids (oxycodone, hydrocodone, hydromorphone, fentanyl, tramadol) will rarely test positive for opioids and will require specific screening.
2. Urine screening can detect metabolites of morphine and heroin within three days of last use and sometimes longer in chronic users.
3. False positive tests can be seen in patients ingesting poppy seeds or taking medications such as quinolones and rifampin.
4. Many substances, including most synthetic or semi-synthetic opioids, are not detected by standard screening panels.
5. See **APPENDIX X, URINE TOXICOLOGY SCREENING**, for further detail.

f. Laboratory data, medical records and information obtained from the PDMP are not reliable tools for the diagnosis of OUD and are best used primarily as adjuncts to screening and to assess adherence to OUD treatment.

4. Obstetrician-gynecologists are encouraged to educate patients that OUD is a treatable chronic disease. Patient education is essential to effective treatment.

a. Patients with OUD may benefit from learning that OUD is a chronic disease centered in the brain but affecting the entire body. Analogies with other chronic diseases like diabetes may help providers communicate the idea that OUD is a chronic disease in which biochemical changes, behavior and medications all contribute to disease management and recovery.
b. Pharmacologic treatment of OUD often benefits patients for months or years. Patients who have previously had MAT regimens prematurely discontinued may mistakenly conclude that MAT is ineffective.
c. Relapse in OUD is common, manageable and not a contraindication to future trials of treatment.
d. Patients on appropriate therapeutic doses of methadone or buprenorphine are cognitively normal and function normally in society.
e. The WHO principles guiding the management of chronic disease apply to the treatment of OUD:
   i. Develop a treatment partnership with patients.
   ii. Focus on patients' concerns and priorities.
   iii. Support patient self-management of illness.
   iv. Use the five "As" at every visit (assess, advise, agree, assist and arrange).
   v. Organize proactive follow-up.
   vi. Link patients to community resources/support.
   vii. Work as a clinical team.
   viii. Involve "expert patients," peer educators and support staff in the health facility.
   ix. Ensure continuity of care.
f. Like other patients with chronic illnesses, patients with SUD may benefit from social supports such as case management, assistance with food, housing, childcare, transportation, job training and legal aid.

5. **It is advised that obstetrician-gynecologists ensure that patients with untreated OUD receive evidence-based treatment with buprenorphine, methadone or naltrexone.**
   a. 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.[694] Methadone, buprenorphine and naltrexone are the three FDA-approved medications for the treatment of OUD.
   b. A Cochrane review and several randomized trials found the addition of counseling to medication conferred no added benefit; MAT plays a central—not adjunctive—role in the treatment of OUD.[695-699]
      i. 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.
      ii. Some patients may desire and/or benefit from behavioral health services. Patients receiving methadone must meet counseling requirements. Clinicians who prescribe buprenorphine are required to be able to refer patients for counseling, but patients are not required to receive counseling.
      iii. Patients with SUD and comorbid depression, anxiety or other behavioral health disorders benefit from multidisciplinary care. Research demonstrates that the treatment of SUD in a patient with behavioral health comorbidities is more likely to be successful if these conditions are treated.[700]
      iv. Obstetrician-gynecologists are encouraged to educate patients that peer support through group meetings can be highly beneficial. Patients should understand that many 12-step and/or abstinence-oriented group programs operate from an outdated understanding of OUD and discourage use of MAT pharmacotherapy. Patients should seek out groups supportive of evidence-based treatment of OUD.
   c. When a patient with untreated OUD is admitted, clinicians are advised to offer pharmacologic treatment. If obstetrician-gynecologists are unfamiliar with how to initiate buprenorphine or methadone, they are encouraged to consult an addiction specialist or hospitalist familiar with initiating MAT. Obstetrician-gynecologists initiating treatment in an inpatient setting may consider that:
      i. If patients are initiated on buprenorphine prematurely, they may experience severe precipitated withdrawal. A careful, collaborative history and clinical assessment decreases the likelihood of precipitated withdrawal. Management of precipitated withdrawal usually involves dosing with additional buprenorphine and adjunctive medication. Failing that, treatment of precipitated withdrawal with a full opioid agonist with strong affinity for the μ-opioid receptor may be appropriate.
      ii. In many communities, treatment with buprenorphine is easier to access.
      iii. It is easy to transition from buprenorphine to methadone in the outpatient setting, whereas transitioning from methadone to buprenorphine poses significant challenges because of the risk of precipitated withdrawal. This fact, as well as buprenorphine's superior safety profile, make it the first-line treatment for OUD initiated in hospital settings.
   d. There are many factors to consider when selecting a MAT agent. **APPENDIX XI, CHARACTERISTICS OF MEDICATIONS USED FOR ADDICTION TREATMENT**, provides further detail on the relative advantages and disadvantages of available pharmacotherapies for OUD. It is advised that the choice of MAT agent be a shared decision with the patient. Decisions in Recovery: Treatment for Opioid Use Disorder is a website for patients that may aid in making informed choices about medication for OUD treatment.

Obstetric Considerations

a. ACOG supports use of methadone or buprenorphine as treatment for OUD in pregnancy.[648] Fewer than two-thirds of pregnant women with OUD receive treatment for OUD in the year prior to delivery, and for women who do receive MAT in pregnancy, rates of discontinuation in the postpartum period are high.[657,701]
b. Pregnant patients with OUD should understand that for the vast majority of patients the benefits of MAT in pregnancy outweigh the risks. Treatment with buprenorphine or methadone improves fetal and infant health compared with untreated OUD.[648-650,702,703] Untreated OUD in pregnancy is associated with poorer fetal outcomes, including increased risk of growth restriction, preterm labor, fetal seizures and miscarriage. Indirect risks include maternal infections (HIV, HCV), malnutrition, poor prenatal care and dangers associated with procuring drugs (e.g., violence, imprisonment).
c. Patients may be reassured that there is no evidence that buprenorphine or methadone increases the risk of birth defects or cognitive impairment.[704]
d. Obstetrician-gynecologists are advised to inform patients of the possibility that their infant may develop NOWS and that this is a common and treatable aspect of MAT in pregnancy (see below).
    i. See **APPENDIX XII, PATIENT-CENTERED DECISION CONSIDERATIONS WHEN SELECTING AN OPIOID AGONIST MEDICATION FOR A PREGNANT PATIENT**, for further information. Colorado's Office of Behavioral Health has created a website, *Tough as a Mother*, with patient education and treatment locators for pregnant and parenting women with SUD.
e. Evidence suggests that the longer the duration of MAT prior to delivery, the more likely women are to continue treatment postpartum. Thus, women with OUD should be encouraged to begin treatment as early in pregnancy as possible.[616]

Naltrexone in Pregnancy

a. There is insufficient evidence for the safety and efficacy of naltrexone in pregnancy to routinely recommend initiating pregnant patients on naltrexone.
b. Initiation of MAT with naltrexone is not advised for pregnant women with active OUD because it requires a period of opioid withdrawal, which exposes women and fetuses to physiologic instability and increases the likelihood of relapse, treatment discontinuation, opioid overdose and death. Treatment with naltrexone is associated with lower treatment retention in nonpregnant populations.
c. Buprenorphine and methadone are easier to initiate and have more evidence supporting their safety and efficacy in pregnancy.
d. Patients who become pregnant while successfully treated on a stable regimen of naltrexone should understand the risks, benefits and alternatives to continuing treatment with naltrexone. It is advised that the decision to continue naltrexone be a carefully weighed, shared decision.
e. While transitioning from one MAT agent to another in pregnancy is discouraged, if the decision is made to change MAT agent, transition from naltrexone to buprenorphine or methadone is best conducted under the supervision of an addiction medicine specialist.
f. Preliminary evidence and some expert opinion suggests that naltrexone use in pregnancy may be safe and effective for select women for the treatment of OUD and/or AUD.
    i. A small retrospective cohort study found that the use of implant naltrexone during pregnancy was not associated with higher rates of congenital anomalies, stillbirth or neonatal mortality, though neonates born to women receiving naltrexone were smaller and had longer hospital stays than infants who were not substance exposed.[705]
    ii. As use of naltrexone for treatment of OUD increases, the need for further research into the safety and efficacy of naltrexone in pregnancy is clear.

Treatment of Opioid Use Disorder continued

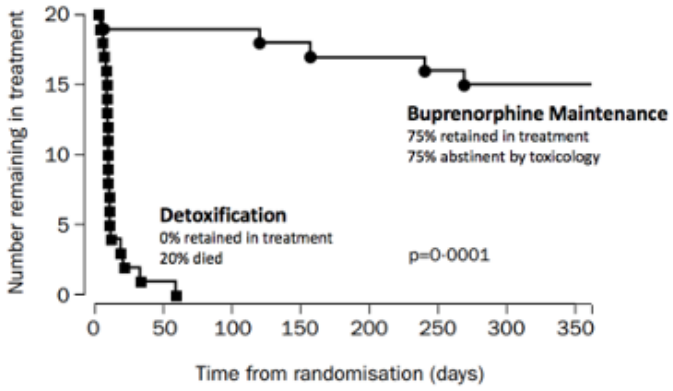
6. **Obstetrician-gynecologists should consider obtaining X-waivers to prescribe buprenorphine for patients with OUD, particularly in practice settings where outpatient MAT is difficult to access.**
   a. Under DATA 2000, physicians are required to have an X-waiver to prescribe and dispense buprenorphine. (Any physician can order buprenorphine to be administered in the inpatient setting to treat acute opioid withdrawal.)
   b. X-waiver training is an eight-hour course for physicians and 24 hours for nurse practitioners (NPs), PAs, CNSs, CRNAs and CNMs. The training is worthwhile even if an obstetrician-gynecologist rarely or never plans to prescribe buprenorphine. It provides valuable information to better understand OUD, MAT and special populations.
   c. X-waivers can be completed online and through several organizations including:
      i. IT MATTTRs
      ii. Providers' Clinical Support System for Medication Assisted Treatment
      iii. ASAM X-Waiver Training
      iv. Waiver Training for Advanced Practice Registered Nurses (APRN)
      v. Waiver Training for Physician Assistants

7. **It is recommended that obstetrician-gynecologists establish relationships with MAT providers to facilitate "warm handoffs" for patients initiated on methadone or buprenorphine in the hospital or clinic setting.**
   a. Obstetrician-gynecologists are encouraged to develop referral networks for patients seen in both clinic and hospital settings so that patients with OUD and other SUDs can be consistently and effectively referred to evidence-based treatment.
   b. A "warm handoff" to an addiction care clinician is more likely to be effective if the appointment is made while the patient is in the clinic or hospitalized. Instructions to call for an appointment at a later time often result in failure to access care.
   c. Office-based opioid treatment (OBOT) programs can offer buprenorphine and naltrexone. They can be associated with addiction medicine practices or embedded in other primary care and subspecialty outpatient providers.
   d. Opioid treatment programs (OTPs), sometimes referred to as methadone clinics, are highly structured and regulated programs that administer methadone or buprenorphine daily on site. For patients who benefit from more structure and added counseling support, OTPs offer a better option than OBOTs. Patients are initially administered either methadone or buprenorphine daily at the facility and have required psychosocial counseling. These facilities are heavily regulated by the DEA, SAMHSA and Colorado's Office of Behavioral Health.
   e. In most urban areas, there exist multiple options for both OBOTs and OTPs that can provide MAT. OpiRescue, a free mobile application and website (https://opirescue.com/), provides an up-to-date MAT treatment locator. It ranks providers based on the distance the patient lives from the provider and gives each provider's treatment options (methadone, buprenorphine or naltrexone). Additionally, SAMHSA (https://findtreatment.samhsa.gov) provides a directory of MAT providers.

8. **Obstetrician-gynecologists are discouraged from endorsing medically supervised withdrawal, "detox" or other abstinence-based treatments for OUD.**
   a. Abstinence-based therapies are largely ineffective for the treatment of OUD.[706] The neurophysiology of opioid dependence is such that willpower is rarely sufficient to override craving for opioids in moderate to severe OUD or to tolerate opioid withdrawal.
   b. Abstinence-oriented treatments have been shown to dramatically increase the risk of overdose when patients relapse. Relapse rates are greater than 80% where treatment is abstinence-based.[707,708]
   c. One study of IV opioid users comparing detoxification vs. buprenorphine maintenance highlights the potential harms of abstinence- and detoxification-related care vs. MAT. In this cohort, zero percent of patients who underwent abstinence-based therapy remained in treatment for over 90 days and 20% died, compared to MAT with buprenorphine, in which 75% remained in treatment at one year with zero deaths.[708]

(FIGURE 9)

One-Year Retention Detox vs Buprenorphine Maintenance



SOURCE: Lancet

d. Medically supervised withdrawal, in which a patient is given a rapid taper of buprenorphine or methadone, is associated with unacceptable rates of treatment failure, relapse and overdose.[706]
e. It is advised that obstetrician-gynecologists inform patients who want to pursue an abstinence-based approach of the increased failure and overdose rates, point out evidence that MAT is more efficacious and work to address potential misconceptions or stigma around MAT.
f. If abstinence is desired by the patient, it is best to achieve this over the course of years and through a very slow and cautious tapering process after stabilization on an opioid agonist. It is still unknown if discontinuation is an appropriate goal as several studies show relapse rates consistently surpassing 50% at one month after discontinuation of buprenorphine therapy.[709-711]

Obstetric Considerations

1. MAT is associated with lower rates of maternal relapse and overdose compared with medically supervised withdrawal and/or treatment without pharmacotherapy.[712-715]
2. Per ACOG,[648] medically supervised withdrawal is not recommended for patients with OUD—including those who are pregnant—as it is associated with high relapse rates, ranging from 59% to more than 90%, and poorer outcomes.[716]
3. Opioid withdrawal puts patients, pregnancies and infants at risk for adverse outcomes. Treatment of OUD in pregnancy should aim to eliminate withdrawal symptoms and the risks associated with illicit opioid use. Medically supervised withdrawal is not advised.
   a. In the first trimester, opioid withdrawal increases the risk of miscarriage. After the first trimester, fetal opioid receptors are fully functional, so maternal withdrawal is accompanied by fetal withdrawal. Clinical and animal studies suggest that fetal withdrawal may have adverse effects on fetal development via adrenergically mediated hypoxia as well as epigenetic alterations of the fetal genome.[683]
4. For patients who refuse MAT during pregnancy after thorough counseling in the risks of withdrawal to the patient and the fetus, medically supervised withdrawal using reduced doses of buprenorphine and methadone can be performed by a physician with experience in perinatal addiction treatment with informed consent from the patient. Intensive outpatient support following medically supervised withdrawal may reduce the substantial risk of relapse.[717]

9. **Obstetrician-gynecologists are encouraged to support the development of hospital MAT protocols and the utilization of a multidisciplinary team approach to initiate MAT.**
   a. ColoradoMAT.org offers free educational materials and protocols that can facilitate development of MAT programs within hospitals.
   b. Several protocols from Project SHOUT are listed in the Appendices:
      i. **QUICK START GUIDE FOR METHADONE – APPENDIX XIII**
      ii. **BUPRENORPHINE QUICK START GUIDE IN PREGNANCY – APPENDIX XIV**
      iii. More complete resources are available on the Project SHOUT website (www.projectshout.org).
   c. In hospitals with addiction medicine specialists, it is recommended that consultation be routine for patients with untreated SUD.
   d. Hospitalized patients with complex medical, pain or addiction histories may warrant consultation by addiction medicine or pain services to plan for safe and appropriate care.

10. **It is advised that patients receiving pharmacotherapy for OUD with methadone or buprenorphine be maintained on their regimens in the setting of acute pain, chronic pain, labor and delivery, elective or emergent surgical intervention and hospitalization.**
    a. Continuing buprenorphine or methadone for OUD treatment improves pain control, reduces the use of opioid analgesia,[718] reduces the risk of relapse,[719] simplifies clinical assessment, avoids withdrawal, decreases the likelihood that a patient will leave against medical advice and obviates the need to restart treatment on discharge.
    b. Rare situations where clinicians should consider modifying dosage or holding medications include:
       i. Severe sedation or respiratory depression. If patient is not sedated but receiving additional sedating medications, obstetrician-gynecologists are advised to monitor closely but not withhold OUD medications.
       ii. QTc>500 on methadone. In the perioperative period, acute illness and new medications can change QTc. Consider decreasing dose of QTc-prolonging medications, including methadone, if QTc is prolonged.
       iii. Newly decompensated liver disease.
    c. Many medications have significant drug interactions with methadone.[720-722]
       i. Drugs that may INCREASE methadone concentration or effect include azole antifungals, some SSRIs, TCAs, erythromycin, ciprofloxacin and quetiapine. If using these medications, obstetrician-gynecologists are advised to closely monitor for sedation and unintentional overdose or consider alternative medications if possible.
       ii. Drugs that may DECREASE methadone concentration include rifampin, many antiretrovirals, phenytoin and carbamazepine. If using these medications, obstetrician-gynecologists are advised to closely monitor for opioid withdrawal or consider alternative medications if possible.
    d. Clinicians are encouraged to verify a patient's MAT dose. OTPs are required to verify doses at any hour of the day or night. Outpatient pharmacy or the patient's outpatient medical record may be of aid if the prescribing clinic cannot be reached.
    e. It is important to confirm with the patient that they have been taking their home dose as prescribed. For patients taking buprenorphine, explain that if they have not been taking their buprenorphine as usual, or if they have been using other opioids, they may experience sudden withdrawal when they restart. Patients tend to disclose nonadherence when they understand the potential for precipitated withdrawal.
    f. It is also important to notify the outpatient buprenorphine or methadone provider of admission and anticipated length of stay so that hospitalized patients are not mistaken as program dropouts and so that continuity of care on discharge is smooth.
    g. If dose adjustments are made during hospitalization, it is critical to inform the outpatient MAT provider.

11. It is advised that patients receiving methadone or buprenorphine for treatment of OUD who are in pain be offered multimodal analgesia and, if needed, opioid agonists.

a. It is recommended that opioid-sparing multimodal analgesic treatment modalities should be first line for all patients, including those on MAT. (For guidance see "Managing Perioperative Pain in Gynecologic Patients Receiving MAT" in **SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE**.)
   i. Although it was previously believed that buprenorphine blocked the effects of full opioid agonists in the setting of acute pain, it is now known that the continuation of buprenorphine does not prevent adequate analgesia from opioids.[718] (Naloxone present in combination products is not bioavailable and does not block analgesia.)

b. Anesthesia or pain service consult may suggest specialized approaches to analgesia in the patient whose pain is not well controlled.

c. Patients should understand that treatment may not alleviate all pain and that manageable pain can be a useful guide to assessment and recovery.

d. Pain is a biopsychosocial phenomenon, and the importance of addressing the affective components of pain cannot be understated. Consultation with social work, psychology or psychiatry may help a patient better manage their pain during a hospital stay. Cognitive and behavioral therapies may reduce pain and anxiety in some patients. It is recommended that case management and psychosocial support be offered to any patient with OUD.

e. It is advised that opioid analgesics be provided to patients when nonopioid multimodal analgesia fails to control pain. Patients taking opioid agonists will have higher tolerance to opioids. The prevalence of OIH is unknown but likely complicates pain management for some opioid-dependent patients.
   i. Opioid-tolerant patients will likely require higher than typical doses of opioids.[344,723] Long-term opioid use produces tolerance and hyperalgesia.[724]
   ii. Obstetrician-gynecologists are advised to avoid prescribing mixed agonists/antagonists such as butorphanol and nalbuphine as they may cause precipitated withdrawal.[724,725]
   iii. Obstetrician-gynecologists are also advised to avoid prescribing codeine and tramadol to breastfeeding patients because of the risk of overdose in the infant.

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

a. As a full opioid antagonist, naltrexone will block the analgesic effects of most opioids. Naltrexone comes in two forms, an oral tablet usually used for AUD and a once-a-month long-lasting depo injection used for OUD.

b. Patients who have been on naltrexone and no longer have it in their system may have lower opioid tolerances than they did previously, so caution is advised.

c. It is recommended that naltrexone be held upon presentation for any acute pain that may require opioids.

d. For elective surgeries where use of opioids is anticipated, it is advised to hold oral naltrexone for 72 hours prior to procedure[106,726] and to hold IM naltrexone for at least 30 days, with oral dose bridging until 72 hours prior to procedure.

e. If naltrexone is still present, it is recommended that pain management center on nonopioid multimodal analgesia including but not limited to NSAIDs, acetaminophen, ketamine and local/regional anesthesia, or conscious sedation with nonopioids as needed. (For guidance see "Managing Perioperative Pain in Gynecologic Patients Receiving MAT" in **SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE**.)
f. If naltrexone is still present and opioids are necessary, high doses of high potency opioids can be used to outcompete naltrexone at the opioid receptor. Animal studies suggest that fentanyl doses may need to be up to 20 times higher than usual doses. It is advised that the patient be closely monitored, at minimum with pulse oximetry and telemetry, to ensure that over-sedation and unintentional overdose does not occur.
g. If opioids are used, holding naltrexone for three to seven days from last opioid dose is recommended.[106,726]

13. Obstetrician-gynecologists are advised to be familiar with the laws, regulations and ethical considerations that govern collecting biological samples for toxicologic testing and reporting of positive toxicology results, as well as the range of social and legal implications for pregnant and parenting patients with positive drug tests.

a. In Colorado, reporting of substance use in pregnancy is not mandatory if the pregnant patient has no children in the home. C.R.S. § 13-25-136 protects pregnant and postpartum patients (up to one year after delivery) from criminal penalty related to positive screening for substance use if no previous children are in the home. The statute also protects pregnant and parenting women who disclose substance use in pregnancy and are seeking or engaged in behavioral health treatment. (Women already involved in child neglect or abuse investigations may not be protected by this statute.) To the extent child abuse reporting is mandatory it is for reporting child abuse, not parental substance use. Parental substance use must be reported when it threatens the health or welfare of the child as defined in statute as "abuse."
b. Fear of loss of custody of their newborn or existing children and/or reporting to child protective services may prompt pregnant women to avoid prenatal care or to conceal substance use.[727] Clinicians are encouraged to educate patients about the provider's reporting obligations and policies, and that obtaining prenatal care and treatment for SUD increases their chances of maintaining custody of their child(ren), so that patients can make decisions about what they disclose and how they access care.
c. Obstetrician-gynecologists are reminded that toxicology testing cannot diagnose SUD or assess its severity. Positive toxicology results may demonstrate recent use of a substance but do not indicate the extent of or frequency of use. Conversely, toxicology may fail to detect sporadic use of a substance or may produce false positives that can be stigmatizing or have serious legal consequences.[728]
d. Rates of false positivity for urine drug screening can be as high as 15%.[729] Confirmatory testing is strongly recommended after a preliminary positive screen and prior to reporting results to any governmental agency.
e. Informed consent is not simply the signing of a form. Rather, informed consent is a process in which a clinician fully educates a patient on the risks and benefits of a test or procedure and the patient freely decides whether or not to undergo the test or procedure. The patient may withdraw consent at any point.
f. Obstetrician-gynecologists are advised to obtain informed consent for urine, blood or saliva toxicology screenings for substance use, and the informed consent process should be documented. Obstetrician-gynecologists are advised to review with the pregnant patient the risks and limitations of each type of toxicologic screen, including the legal risks. Patients should be advised that false positive and false negative results are possible and that confirmatory testing may be needed.

g. Obstetrician-gynecologists may educate patients that they do not perform screenings out of distrust or punitive motives, but rather to establish an accurate baseline of substance use. Patients may be further advised that many people are unaware of the exact composition of the substances they use and that test results will be used to ensure that the patient receives the best care possible.
h. Obstetrician-gynecologists are strongly discouraged from performing tests for nonmedical reasons. Obstetrician-gynecologists are not required to perform tests that are requested by outside parties for nontherapeutic reasons, (e.g., courts, child protective services, workplaces or treatment programs.) Performing tests for nonmedical reasons erodes patient trust in clinicians and the health care system. In all cases, the principles of informed consent apply, and patients must be informed that a test is being performed for nonmedical reasons.
i. Clinicians are reminded that tobacco and alcohol use disorders carry as much or more risk in pregnancy as OUD does, and the prevalence of alcohol and tobacco use are far higher than those of illegal-substance SUD.[730] Focus on screening for illicit substances must not distract from the profound harms to both pregnant women and their fetuses that alcohol and tobacco cause. Regardless of substance, a harm-reduction approach that meets the patient where they are at is recommended, and the risks of any substance use should be considered in context and in relationship to other social-determinants of health.

Colorado Law Pertaining to Nonmedical Use of Substances in Pregnancy

1. The federal Child Abuse Prevention and Treatment Act (CAPTA) requires states to have policies in place to address the needs of neonates identified as affected by maternal SUD and those with NOWS or other substance withdrawal symptoms, including a plan for notification to child welfare of identified neonates and development of a plan of safe care if needed. Notification need not be the same as a child abuse report. A plan of safe care need not be the same as a "safety plan." It is up to states to determine when a plan is needed and who is responsible. CAPTA also requires states to have treatment available for substance-exposed infants and for the family members or caregivers with SUD. How Colorado is interpreting these provisions of CAPTA continues to evolve; a 2019 report identified Colorado as not fully compliant.[731]
2. C.R.S. § 13-25-136 prevents criminal prosecution of pregnant women who disclose use of scheduled substances to their prenatal care provider and/or have a positive toxicology screen during the prenatal period, and clinicians are bound by the rules of ethics not to disclose private medical information.
3. Some hospitals test babies after birth for drugs, though providers are not required to do so, and such testing is not required by CAPTA.
4. Colorado law with regard to child abuse and prenatal substance use changed in 2020 through SB 20-028, which amended C.R.S. § 19-1-103 and 19-3-102, and is no longer based on toxicology results. Abuse is now defined as when a child is born "affected by" exposure to either alcohol or drugs (unless they are prescribed or recommended, thus providing exemption for cannabis and methadone or buprenorphine as treatment for OUD) AND the newborn's health or welfare is threatened by the substance use.
5. Clinicians, as mandatory reporters, do have a duty to report known or suspected child abuse under C.R.S. § 19-3-304, so they will have a duty to report when a child is born fitting the above two-pronged condition. The details of this will be further developed through rules promulgated by the Board of Human Services.
6. Colorado obstetrician-gynecologists can advocate and help ensure that these rules are developed with the treatment needs and best interests of their patients in mind.

Treatment of Opioid Use Disorder continued

14. It is advised that pregnant patients with OUD be counseled about the possibility that their infant will experience NOWS, and equipped with the knowledge and skills needed to assist in caring for their infant if the infant needs treatment for NOWS.

a. Symptoms include irritability, high-pitched crying, poor sleep and uncoordinated sucking reflexes. Timing of onset of NOWS depends on the opioid to which the infant was exposed. Symptoms will usually begin within two to three days for infants exposed to short-acting opioids (heroin, oxycodone, fentanyl) and within four days for infants exposed to long-acting agents.

b. Prior to delivery, pregnant women with OUD should establish care with a neonatologist or pediatrician experienced in managing NOWS.

c. While differences in incidence, severity and duration of NOWS in buprenorphine- versus methadone-exposed newborns is not clearly established, studies do suggest that prolonged skin contact, nursing and other forms of parental soothing dramatically ameliorate symptoms of NOWS and reduce length of stay, opioid requirements and health care costs. Obstetrician-gynecologists are advised to advocate for rooming-in models to support intensive maternal-infant contact.[683]

d. While management of NOWS is outside the scope of these guidelines, the CHoSEN network offers a searchable Colorado Perinatal Substance Use Provider Toolkit for clinicians with Colorado-specific resources related to patient identification and communication, SUD treatment, lactation, management of substance-specific impacts, community referrals, patient education and more. Video resources for clinicians are offered in a clinician video library. The CHoSEN collaborative quality improvement resources for clinicians and institutions provide templates for Eat, Sleep, Console (ESC) protocols and other nonpharmacologic approaches to NOWS, prenatal counseling, breastfeeding and discharge planning.

e. In Colorado, the CHoSEN network has produced video educational materials about NOWS for pregnant women and their families.

15. It is advised that women with OUD who are on stable treatment regimens be encouraged to breastfeed and that women with active SUD who wish to breastfeed be offered lactation consultation to maintain their milk supply while they are supported in their efforts to enter treatment and recovery.

a. Breastfeeding promotes maternal-infant bonding, provides ideal neonatal nutrition and, in addition to the many well-established health benefits to both woman and infant, breastfeeding may diminish the severity and duration of NOWS. In addition, breastfeeding may be protective against sudden infant death syndrome, which is more prevalent in substance-exposed newborns.[683]

b. ACOG supports breastfeeding in women who are stable on their opioid agonist, not using nonmedical drugs and have no contraindication, such as HIV infection.[648]

c. Divided doses of MAT agent during breastfeeding may ensure a more consistent level of neonatal opioid ingestion. Careful monitoring of methadone serum level and neonatal level of sedation are necessary in the postpartum period as pregnancy-induced accelerated metabolism rapidly reverses.

d. HCV infection is not a contraindication to breastfeeding except in cases of nipple trauma where exposure to the mother's blood is a possibility.

e. It is recommended that patients receiving MAT who have evidence by history or toxicology testing of active or recent use of nonprescribed substances at time of delivery as well as patients with active, untreated OUD or polysubstance use disorder (including cannabis use)[732] receive lactation consultation and be offered resources for addiction care. Patients may be offered instruction and materials to pump and discard breast milk so as to maintain their milk supply until they meet criteria for safe breastfeeding.[648,733,734]

16. The postpartum period is one of increased vulnerability for patients with OUD (whether or not they are receiving MAT), and it is advised that a comprehensive treatment plan be designed to meet the specific needs of the maternal-infant dyad.

a. Women with SUD frequently experience poverty, IPV, behavioral health comorbidities and poor access to medical care. The postpartum period may exacerbate these factors, increasing likelihood of relapse and poor outcomes for mother and infant.[735,736]

b. Resources for pregnant patients with OUD are relatively abundant compared to those available to women in the postpartum period, despite the fact that for many women, postpartum mood disorders, sleep disturbances, and the challenges of parenting increase risk of relapse and/or severity of OUD. The treatment resources available to pregnant women often end a few months postpartum.

   i. In many states, Medicaid may be available to women for only two months postpartum. More than one-third of U.S. methadone clinics do not accept Medicaid. While many of them offer discounted fees or incentives for pregnant women to stay in treatment, few do so for postpartum women. In addition, the requirements for daily visits to an OTP pose a major barrier to access for women who are newly caring for an infant, many of whom lack transportation and strong social supports. Interventions to increase treatment retention with voucher-based incentives have not shown dramatic improvements.

   ii. Health First Colorado offers "Special Connections,"[737] a program for pregnant women with drug or alcohol addiction, which extends care from the 60 days postpartum typically covered by Health First to a full year and includes residential treatment services not otherwise covered by Medicaid. Note that women must enroll in Special Connections prior to delivery. The program is available to women who are:

      1. Eligible for Health First Colorado
      2. Pregnant or within one year after delivery (only women who were in Special Connections before they delivered are eligible for Special Connections services after they deliver)
      3. At risk of having an unhealthy pregnancy and unhealthy baby because of alcohol and/or drug abuse problems

   iii. The program offers benefits and services that ideally would be offered to all women with OUD, including:

      1. Case management
      2. Group health education with other pregnant women
      3. Individual counseling and group SUD counseling with other pregnant patients
      4. In-depth risk screening, urine screening and monitoring
      5. Referral to appropriate aftercare and ongoing support

c. New mothers with postpartum depression are at high risk for substance use and/or relapse.[738] It is recommended that women be screened at every visit for postpartum depression and for exacerbations of other behavioral health conditions as appropriate.

d. Rates of binge substance use are higher in the postpartum period than during pregnancy.[668]

e. Societal pressures, threat of loss of custody and pronounced stigma against SUD in women with infants prompt women to conceal or deny substance use.

f. Ideally, home visits by a nurse, postpartum doula, social worker, child welfare specialist, nutritionist and/or other professional supports will be made available to women and infants in the postpartum period.

g. It is advised that dose adjustments of methadone or buprenorphine be carefully managed in the postpartum period by an addiction medicine specialist. Risks of relapse and overdose are higher in the postpartum period than in pregnancy for women with OUD. Careful patient monitoring and support is critical.

h. Though reliable data are lacking, the few existing studies find rates of treatment discontinuation of between 11-64% in populations of women receiving methadone before and after birth.[616]

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 system capable of serving the needs of all patients impacted by the opioid epidemic.

2. **Repeal the X-waiver requirement for prescribing buprenorphine.**
   a. It is not in the public's best interest to require clinicians to have a waiver to treat patients with OUD, especially when no such waiver is required to *prescribe* opioids.
   b. While more than 900,000 U.S. physicians are licensed to write prescriptions for opioids, fewer than 32,000 are authorized to prescribe buprenorphine for the treatment of OUD.[739]
   c. The waiver requirement is a barrier to treatment and adds to the stigma surrounding OUD.
   d. Repeal of the X-waiver requirement is endorsed by the WHO, the American College of Emergency Physicians, the American Academy of Clinical Toxicology and ASAM.
   e. Similar deregulation has enabled the widespread use of buprenorphine in France, which has led to a 79% decline in the country's opioid overdose deaths since 1995.[740]
   f. Legislation designed to eliminate the requirement for clinicians to obtain a DEA waiver to treat OUD with buprenorphine, such as the Mainstreaming Addiction Treatment Act (U.S. HR 2482), should be supported. Elimination of the waiver requirement will greatly aid efforts to close the treatment gap for OUD.

3. **Ease regulations around 42 CFR Part 2 to facilitate the sharing of critical health data.**
   a. 42 CFR Part 2 requires any patient with SUD to provide explicit permission for a treating provider to share information about their medical care, even with other clinicians involved in their treatment.
   b. 42 CFR provided an essential safeguard for privacy from 1975 until HIPAA was enacted in 1996. However, 42 CFR Part 2 has created two separate, poorly aligned systems of care that often place patients in danger.
   c. OTPs that treat patients with methadone and buprenorphine cannot disclose this fact to other health care professionals; as a result, many primary care clinicians, specialists and hospital-based physicians are left unaware of a patient's maintenance on methadone.
   d. In addition, methadone and buprenorphine dispensed from OTPs are not recorded by the Colorado PDMP, a fact which significantly undercuts the utility of the PDMP.
      i. As of July 2020, per SAMHSA's 42 CFR Part 2 Revised Rule, "OTPs are permitted to enroll in a state prescription drug monitoring program (PDMP), and permitted to report data into the PDMP when prescribing or dispensing medications on Schedules II to V, consistent with applicable state law." While this represents progress toward aligning addiction care with standard medical practice, SAMHSA should further revise the rule to mandate OTP reporting to PDMPs for all patients. Patients should not have to give consent, and OTPs should be required to report medications dispensed to the PDMP. In the interim, OTPs should actively encourage their patients to consent to reporting and should report patient medication use to the PDMP.
   e. Lack of clinician access to patient medication information proves dangerous when physicians prescribe QTc-prolonging drugs, benzodiazepines and other medications that interact with methadone.
   f. Separating SUD from the rest of medicine further stigmatizes a disease process that might otherwise be normalized.

g. CO's CURE 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-physician relationship.
h. CO's CURE joins the AMA, the American Hospital Association, ASAM and others in the call to better align SUD treatment with the rest of medicine.

4. **It is recommended that telemedicine for addiction treatment be widely available and that telemedicine clinicians be permitted to prescribe buprenorphine without a face-to-face encounter.**
   a. The 2018 Special Registration for Telemedicine Clarification Act directs the DEA to amend its rules regarding the face-to-face encounters required by the 2008 Ryan Haight Act when prescribing controlled substances.
   b. The Ryan Haight Act prevents clinicians from treating patients with OUD in rural areas and unnecessarily hinders 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. CO's CURE encourages a loosening of these restrictions to allow clinicians to better treat patients with OUD in rural and other hard-to-access areas.

5. **Decrease the regulations surrounding OTPs to reduce barriers for methadone maintenance treatment.**
   a. To be enrolled in an OTP and receive treatment with methadone, a patient must have been using opioids for at least 12 months. It is recommended that no patient be required to wait 12 months for treatment for a life-threatening disease.
   b. It is suggested that counseling adherence requirements within OTPs not be a condition of medication receipt. While most patients benefit from case management and counseling, patient autonomy is violated by the rigid requirements mandated by state and federal regulations.
   c. It is advised that a patient's ability to access proven medications like methadone and buprenorphine never be conditional upon other treatment modalities. There are many other disease states that would benefit from psychosocial therapy in addition to medication management, but it would never be acceptable to make one a requirement of the other.
   d. Allow NPs to have a full scope practice within OTPs. Current regulations prohibit NPs from ordering methadone within an OTP. No such medical restrictions exist outside of OTPs.

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

7. **Encourage the creation and continued funding of centers where obstetric, addiction, pediatric and behavioral health services are co-located and connected to rural and telemedicine options so people have multiple points of access.**
   a. SUD is a chronic, relapsing disease. Women with SUD and their infants remain at risk of the adverse health and social effects of relapse indefinitely.
   b. Co-location of providers facilitates the early detection and treatment of behavioral and medical problems.
   c. Federal, state and local resources should support the creation of comprehensive co-located services for women and families in rural and underserved areas of Colorado.

Treatment of Opioid Use Disorder continued

8. **Mandate that private and public insurers expand the range of services and extend the duration of coverage for addiction care and behavioral health services from the traditional six-week postpartum period to one year or more, and align billing with patient needs and best practices.**
   a. While many medical and social supports are available to pregnant women with OUD, roughly half of births in the United States are covered by Medicaid, which insures the cost of treatment for OUD for only six weeks postpartum. The disruption in care that can occur as a result of insurance limitations during the postpartum period can be devastating.
   b. Support increased reimbursement for SUD screening and integrated comprehensive care for prenatal, peripartum and postpartum care of women with SUD.
   c. Improve billing so that services are not interrupted due to lack of billing codes.

9. **Improve care for pregnant people with OUD by improving care for all pregnant people and for all people with SUD.**
   a. Evidence suggests that policies, including public health messages, that specifically target pregnant people do more harm than good, while policies and messages that apply to the general population do not have the same negative unintended consequences.[741] For example, warning label initiatives (e.g., for alcohol, tobacco and cannabis) that are directed at pregnant people fail to change behavior in pregnant people with SUD but do deter them from seeking prenatal care and providing a full substance use history, and such policies are associated with poorer pregnancy outcomes.[742]
   b. Address gaps in access to care for all pregnant people in Colorado. Many must travel long distances for care, and even then many do not have access to the care they need or desire. For some women, culturally congruent clinicians are simply unavailable. There are numerous factors that further underpin the inadequacy of prenatal care options for many women in Colorado, including lack of diversity among clinicians, inadequate reimbursement rates, high malpractice insurance costs and lack of integration of midwives.
   c. Address inequities in outcomes by addressing racism and income inequality directly, both in and outside of the health care system. Racism and income inequality are associated with negative health outcomes not only for Black and Indigenous pregnant people but also low-income white people,[743] who are disproportionately impacted by OUD. Support legislation like the Police Accountability Act passed in 2020, and acknowledge the intersection of societal factors and issues that impact people's health.
   d. Support increased access to community-based, culturally congruent doulas and certified professional midwives and birth centers.
   e. Collaborate on efforts to identify gaps and trends through data, increase use and disclosure of data as a quality improvement mechanism, and support and expand maternal mortality and morbidity reviews.
   f. Support paid family leave and childcare initiatives that help caretakers (who are disproportionately women) remain healthy and economically stable.

The Future and Ending the Opioid Epidemic in Colorado

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

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

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

On behalf of our sponsoring organizations—CHA, Colorado Medical Society and Colorado Consortium for Prescription Drug Abuse Prevention—as well as the Colorado section of ACOG and the 11 other medical specialties that have stepped forward to participate, we offer our gratitude and appreciation for the care and consideration you give these guidelines. The health of our state and its people depends on clinicians and leaders like you who are willing to be agents of change. Together we can make a profound difference in the lives of Coloradans as we implement new, better standards of care. Together we can bring this deadly epidemic to an end.

Debra Parsons, MD, FACP
PRESIDENT, COLORADO MEDICAL SOCIETY

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

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

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

Appendices

I. The Clinically Aligned Pain Assessment (CAPA)

II. Risk Index for the Prediction of Chronic Post-surgical Pain

III. Understanding Pain: A Complex Biopsychosocial Phenomenon

IV. Cannabinoids and Pain

V. Risks, Benefits and Contraindications of Peripheral Nerve and Plane Blocks

VI. Peripheral Nerve and Plane Blocks for Common Obstetric and Gynecologic Surgical Procedures

VII. Primary and Adjunctive Pharmacologic Agents for Regional Anesthesia

VIII. Map and List of Syringe Access Programs in Colorado

IX. Intimate Partner Violence Screening Questions

X. Urine Toxicology Screening

XI. Characteristics of Medications Used for Addiction Treatment

XII. Patient-Centered Decision Considerations when Selecting an Opioid Agonist Medication for a Pregnant Patient

XIII. Quick Start Guide for Methadone

XIV. Buprenorphine Quick Start Guide in Pregnancy

Appendix I

The Clinically Aligned Pain Assessment (CAPA)[114]

Domain	Response
Comfort	Intolerable
	Tolerable with discomfort
	Comfortably manageable
Change in pain	Getting worse
	About the same
	Getting better
Pain control	Inadequate pain control
	Partially effective
	Full effective
Functioning	Cannot do anything because of pain
	Pain keeps me from doing most of what I need to do
	Can do most things, but pain gets in the way of some
	Can do anything I need to do
Sleep	Awake with pain most of night
	Awake with occasional pain
	Normal sleep

CAPA is designed to assess pain more effectively, in a clinically valid way, and to have more dialog with the patient about their pain experience. Printed with permission, University of Utah Hospital and Clinics/Department of Anesthesiology. CAPA, Clinically Aligned Pain Assessment (43).

SOURCE: Gordon DB. Acute pain assessment tools: let us move beyond simple pain ratings. Curr Opin Anesthesiol. 2015[114]

Appendix II

Risk Index for the Prediction of Chronic Postsurgical Pain[187]

Please ask the patient before surgery: no/yes

1.	Have you suffered form preoperative pain in the part of the body operated on?	<0.001	4.80
2.	Have you suffered from preoperative pain elsewhere (chronic headache, back pain, etc.)?	<0.003	2.80
3.	Have you felt hopelessness, sadness or depression lasting longer than two weeks in the past 6 months?	<0.166	1.61
4.	Considering the last 6 months, have you felt extremely nervous and /or anxious?	<0.067	1.88
5.	Have you suffered from capacity overload/overstrain in the past 6 months?	<0.006	2.61
6.	Do you suffer from any of the following symptoms: - Sleeping disorder, exhaustibility/exhaustion, frightening thoughts, dizziness, tachycardia, feeling of being misunderstood, trembling hands, or do you take any sleeping /sedation pills. (the item is assessed positive if the patient suffers from two or more symptoms)	<0.001	3.40
7.	How do you see your convalescence? Do you think you will be fit for work again or to do your daily activities within the next 6 months? (belief that no recovery/resumption is possible after months)	<0.096	2.70
8.	Does the surgery imply an increased risk of nerve injury (thoracotomy, mastectomy, hernia repair, abdominal surgery, etc.)?	<0.075	0.53
9.	Does the patient undergo a removal/revision surgery or a primary surgery?	<0.699	1.17
10.	Will a non-laparoscopic or minimally invasive surgery be performed?	<0.005	0.34
11.	Will a mesh implantation be performed?	<0.089	0.32
12.	Is it inpatient (or ambulatory) surgery?	<0.033	9.49

To score: (1) 0 or 1 risk factors presented = low risk of developing CPSP, (2) 2 risk factors presented = moderate risk of developing CPSP, (3) 3-5 risk factors presented = high risk of developing CPSP.[187]

SOURCE: Gordon DB. Acute pain assessment tools: let us move beyond simple pain ratings. Curr Opin Anesthesiol. 2015[114]

SOURCE: CDC/AHA Opioid Factsheet for Patients

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 chronic 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 the patient's 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.[744-746]

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.[747-749] 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.[750] Studies have also identified measurable electroencephalographic signatures capable of predicting differences in pain tolerance between individuals.[751]

The Psychology of Pain

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

The context of a painful stimulus and a person's prior life events further influence the way in which they experience pain. For example, a person who grew up loving dogs is at home with their new puppy. If they are suddenly nipped in the middle of the night with an intensity of "x," they will experience pain. However, their prior positive interactions with dogs, the safe surroundings (home) and their certainty that the nip came from the puppy will modulate the negativity of the experience. The same person, who has always been wary of the ocean, is now at the beach. After finally mustering the courage to wade in, they hear a lifeguard shout, "Shark!" If they feels a nip at their ankles while in the water, they are likely to have a drastically different pain experience than they had with the puppy—even if the intensity of the two experiences is identical.

The anticipation of pain and expectations surrounding painful experiences as well as expectations of relief impact the experience of pain on neuroimaging and by patient report. Studies of normal subjects demonstrate the power of both the placebo effect and the nocebo effect; the same noxious stimulus can produce markedly different neuroimaging and patient experiences. Accordingly, a host of psychological interventions have demonstrated evidence for relieving the negative effects of the pain experience. These include the use of supportive therapy, CBT, acceptance and commitment therapy, virtual reality therapy and mindfulness-oriented interventions, which leverage insights into the cognitive and affective components of pain signaling.

The association between mental health and SUD and the experience of pain is well established.[752] 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.[753-755]

Finally, it is important to acknowledge the critical role that clinician empathy can play in promoting pain relief.[756] 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.[757] 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.[758] 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.[759]

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

Cannabinoids and Pain

Cannabinoids and Pain: Counseling Patients

- As of this writing, no definitive, high-quality studies support the safety and efficacy of dispensary or pharmaceutical cannabinoids for analgesia in chronic noncancer pain. Until better evidence is available, physicians are discouraged from endorsing the use of cannabinoids for pain management. No evidence supports the efficacy of cannabinoids for acute pain. Patients may be counseled that research suggests that chronic use of cannabis may in fact complicate pain management.[720,721]
- It is recommended that any patient with chronic pain be encouraged to seek care from a pain medicine specialist.
- It is suggested that patients be counseled that the use of any drug that lacks rigorous FDA drug development and safety profiles carries inherent risks.
  - The testing and regulation of dispensary cannabis is poor to nonexistent.
  - Products purchased at dispensaries may be mislabeled, of undetermined content and/or contaminated with harmful substances.
  - It is important to remind patients that cannabis dispensary workers are not trained or qualified to give medical advice.
- Adverse effects associated with cannabinoid use include:
  - The development of cannabis use disorder (CUD)
    - Historically, one in 10 cannabis users—and one in six users under the age of 18 years—will develop CUD.[692,693]
    - 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%.[694]
    - CUD is associated with an increased likelihood of developing other SUDs.[695]
  - Cognitive and behavioral
    - Short-term adverse effects include deficits in attention, memory and learning. Chronic use of cannabinoids may cause permanent cognitive deficits.[696,697]
    - Daily use or high doses of Δ9-tetrahydrocannabinol (THC) can cause anxiety, paranoia and psychosis. Chronic cannabis use is associated with an increased risk of developing schizophrenia.[698-707]
    - Cannabis use is associated with higher rates of depression, anxiety and suicidality.[708-710]
  - Cardiovascular
    - Smoking or vaping cannabinoids increases the risk for stroke and heart disease.[711-714]
  - Pulmonary
    - Smoking or vaping cannabis in any form can harm lung tissues, scar small blood vessels and expose patients to many of the same toxins, irritants and carcinogens found in tobacco smoke.[715,716]
    - Second-hand cannabis smoke is harmful to the health of exposed contacts, particularly children and adolescents.[717]
  - Malignancy
    - Chronic cannabis use may increase the risks of testicular cancer and human papilloma virus (HPV)-related head and neck squamous cell carcinoma (HNSCC).[718,719]
- Pregnant or breastfeeding patients are strongly advised to avoid cannabis use due to known and unknown risks to the developing brain. The potential exists for birth defects, possible autism or spectrum disorders and other behavioral abnormalities in children of women who use cannabinoids in the perinatal period.[722]
- Despite the cautions above, medical clinicians may counsel their patients that many physicians, researchers, the AMA and the organizations represented in CO's CURE advocate for rigorous scientific research into the safety and efficacy of cannabinoids for pain management.

Introduction

The opioid epidemic has motivated physicians, researchers and patients to seek alternatives to opioids for the management of pain. Legalization and wider societal acceptance of cannabinoids, a broad term that describes the drugs derived from the plants of the genus Cannabis, has prompted some to ask whether cannabinoids might offer a safer, less-addictive alternative to opioid analgesia. While cannabinoids carry little risk of overdose death, their opioid-sparing potential and analgesic efficacy are unproven. Two ecological studies raised the possibility that medical cannabis legalization might reduce the use of opioids and rates of overdose death; however, subsequent individual-level research has challenged this hypothesis, and some states have seen rates of opioid-related harms increase after enactment of medical cannabis legislation.[791-793]

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.[794] Evidence regarding the efficacy of cannabinoids, including dispensary cannabis, for the management of acute pain is nonexistent.[761] 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.[795-797]

Though cannabinoids have been studied for decades, the barriers to cannabinoid research are many. In particular, plant-derived cannabinoids in the United States are classified as Schedule I substances for which research is tightly regulated. Furthermore, the pharmacokinetics of these substances are complex and depend on the composition of the synthetic or herbal product and the route of administration. The chemical content of unprocessed botanical cannabis varies significantly; there are more than 100 pharmacologically active cannabinoids, the most widely studied of which are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). (The remaining cannabinoids and terpenes contribute to the smell, taste and possible pharmacologic effects of cannabis).[798] 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.[799] 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."[800]

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.[795,796,801-804] The human endocannabinoid system is composed of the cannabinoid receptors CB1 and CB2 and the endogenous human cannabinoids N-arachidonoylethanolamine (AEA), also known as anandamide, and 2-arachidonoylglycerol. CB1 receptors are concentrated in presynaptic neurons in areas of the brain that regulate appetite, memory, fear and motor responses, as well as in the spinal cord, dorsal root ganglia, the GI tract, liver, fat cells and skeletal muscle, while CB2 receptors are primarily found in macrophages and tissues that modulate inflammation.[778,805]

Both cannabinoid receptors and endocannabinoids are involved in the regulation of pain sensation, with modulatory actions at all stages of pain processing pathways.[806] 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.[796] Both μMu-opioid receptors and CB1 receptors are found in the dorsal horn of the spinal cord at the first synaptic contact for

peripheral nociceptive afferent neurons.[807,808] 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.[795,796,809]

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 VAS 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.[797]

These findings of the Stockings review closely mirror those of a 2018 Cochrane review (Mücke) of cannabinoids for the treatment of chronic neuropathic pain, which similarly concludes that "there is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain," while noting a high incidence of adverse effects.[810] A subsequent 2019 scoping review (Pratt) assessed data from 72 systematic reviews of medical cannabinoid use.[811] 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.[811] 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.[811] 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.[812] A retrospective review of adolescent ED and urgent care visits found a significant increase in cannabis-associated visits.[813] Another retrospective review found significant increases in cannabis-related hospitalizations, ED visits and poison center calls in Colorado both after local medical

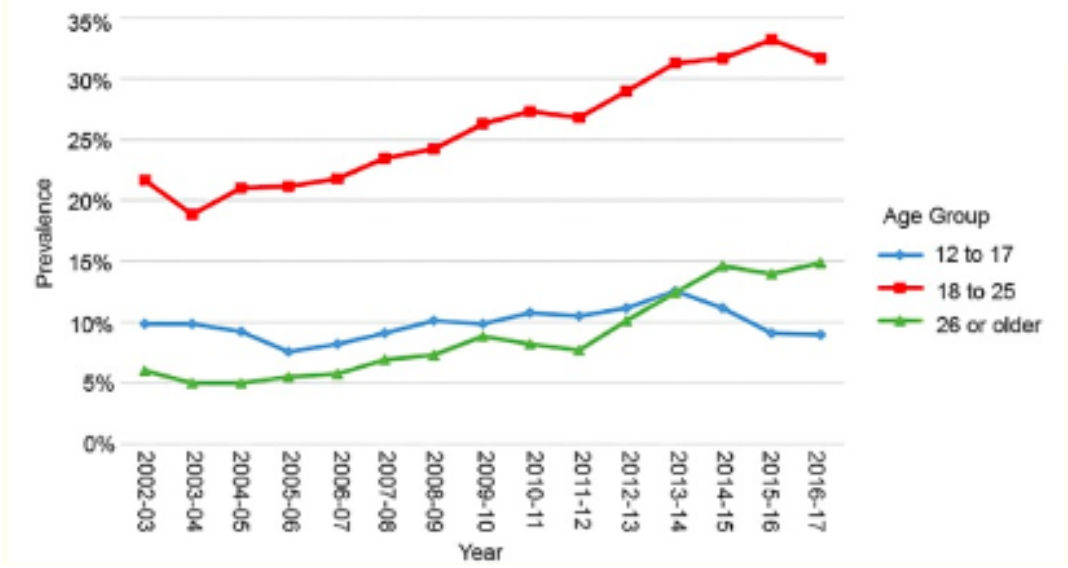
marijuana policy liberalization and after local recreational legalization. Of note was the high prevalence of mental illness presenting in patient visits' cannabis-related codes, an association that warrants further investigation.[814]

While the long-term adverse effects of cannabinoids require further research, a number of studies have associated THC exposure with the later development of schizophrenia,[768-777] depression,[779,781] anxiety[778] and suicidal ideation, attempts and completion.[780] A large prospective cohort study also linked cannabis use to a substantial risk for the later development of CUD,[815] estimating that 9% of adults and 17% of adolescent users will develop the disorder.[762] Both gray- and white-matter changes have been found in chronic cannabis users, as have volume reductions in the amygdala and hippocampus.[766,816-819] National reporting systems and rigorous research into the short- and long-term adverse effects of cannabinoids are urgently needed.

Clinicians in Colorado are likely aware of the high incidence and prevalence of cannabis use in the state **(FIGURE 10)**. An estimated 39% of patients who receive chronic opioid therapy for pain report also using cannabis.[820,821] When the opportunity arises, clinicians are encouraged to advise patients that current evidence does not support the use of cannabis as a safe, effective analgesic and that further research is warranted. It is recommended that patients with chronic pain who inquire about cannabis for analgesia be referred to a pain management specialist.

(FIGURE 10)

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[822]

Appendix V

Risks, Benefits and Contraindications of Peripheral Nerve and Plane Blocks

Benefits of Peripheral Nerve and Plane Blocks	Contraindications and Risks
1. Reduce requirements for systemic analgesics **2.** Provide optimal anesthesia for: - Patients at risk of respiratory depression related to systemic or neuraxial opioids (e.g., obstructive sleep apnea, severe obesity, underlying pulmonary disease, advanced age) - Patients with another indication to minimize opioid use (e.g., in recovery with h/o OUD, h/o ORADEs) - Ambulatory surgical patients who may benefit from prolonged profound analgesia (using long-acting LA or continuous PNB) - Patients with h/o acute, severe pain, poorly managed with systemic medication **3.** As an alternative to neuraxial, fascial plane blocks have less risk of neurovascular injury. Optimal analgesia for: - Patients with coagulopathies or those anticoagulants or antiplatelet agents (Note: these patients are candidates for blocks in compressible locations only.) - Patients for whom sympathetic blockade may cause hemodynamic problems (e.g., aortic stenosis) - Patients at elevated risk of urinary retention (e.g., age>65, male, benign prostatic hyperplasia, diabetes, hypertension, history of urinary tract disease or surgery)	**1.** Absolute contraindications include: - Patient refusal - Allergy to local anesthetics - Active infection at the site of injection **2.** Relative contraindications include: - Patient with coagulopathy or receiving antithrombotic medication, especially if blocks are in a noncompressible location (e.g., paravertebral, lumbar plexus, proximal sciatic nerve block) - Preexisting neurologic pathology or deficits in the distribution of the block - Caution with local anesthetic doses in patients with hepatic dysfunction - Doses listed are for adults, and it is recommended that they be reduced in patients with low ideal body weight or in children. It is advised that risks be discussed with the patient and consent obtained. Risks include: - Nerve injury - Vascular injury, bleeding and hematoma - LAST, including seizure and cardiac arrest - Injury to adjacent structures such as bowel, lung, solid organs - Infection

Appendix VI

Peripheral Nerve and Plane Blocks for Common Obstetric and Gynecologic Surgical Procedures[185,823-827]

For All Blocks:

- Most blocks do not provide coverage for visceral pain and, thus, are more useful for managing postoperative pain than as a sole anesthetic technique.
- Strongly consider the use of ultrasound guidance or direct visualization for all blocks.
- Most require large volumes of local anesthetic, with a typical injection volume of 15-30 mL per side.
- Amide anesthetic, preferably ropivacaine 0.5% or bupivacaine 0.5%.Ropivacaine 0.2% and bupivacaine 0.25% are satisfactory alternatives in low body weight individuals.
- Counsel patients on the risks associated with blocks, including vascular and neural injuries, abdominal visceral injury, solid organ injury, pneumothorax/hemothorax, transient sensory or motor blockade, infection and incomplete block.
- It is recommended that a discussion of risks and benefits of regional anesthesia be tailored to the specific needs of the patient and procedure.

Name	Descriptions and Applications	Details and Considerations
Pudendal[828]	**Description:** Provides anesthesia to lower vagina, perineum, anus, clitoris and vulva. **Applicable Surgeries / Procedures:** • Analgesia for the second stage of labor • Operative vaginal delivery • Episiotomy or perineal laceration repair • Minor surgeries of the lower vagina and perineum • CPP diagnosis, treatment • Vulvodynia[370]	Pudendal nerve block does not abolish sensation to anterior perineum, cervix or upper vagina. Injection of local anesthetic is performed at the trunk of the pudendal nerve at the level of the ischial spine. There are transperineal and transvaginal approaches, transvaginal approach most common. For transvaginal approach – a tubular introducer is used, the tip is placed against the vaginal mucosa and just beneath the tip of the ischial spine. Needle passes through sacrospinous ligament into loose areolar tissue where pudendal nerve courses. Anesthetic usually deposited at sacrospinous ligament and into areolar tissue. Block is usually performed bilaterally. Does not interfere with uterine contractions, but may result in loss of bearing-down reflex.[829]

Appendix VI continued

Name	Descriptions and Applications	Details and Considerations
Paracervical[830]	**Description:** Provides anesthesia to the uterovaginal plexus, providing anesthesia to upper vagina, cervix and lower uterus. **Applicable Surgeries / Procedures:** • Analgesia for first stage of labor • Hysteroscopy • D&C • Surgical abortion • Nulliparous or difficult IUD placement • Loop electrosurgical excision procedure (LEEP) • Cervical ablation or excision • Laparoscopic hysterectomy	Blocks sympathetic, parasympathetic and visceral sensory nerves. Does not affect motor pathways and hence does not slow progression of labor or motor function to the legs.[831] For gynecologic procedures vasoconstrictive agents epinephrine/vasopressin improve potency of block, duration of analgesia and decrease bleeding. Vasoconstrictors contraindicated for obstetric procedure. Fetal bradycardia can occur in as many as 15% of paracervical blocks,[832] thought to be secondary to drug-induced arterial vasospasm. Block not recommended in potential fetal compromise. 10 to 20 mL of local anesthetic is injected at the cervicovaginal junction. There are two- and four-point injections. Two-point injection occurs at 4 and 8 o'clock. Four-point injection at 2, 4, 8 and 10 o'clock.

Appendix VI continued

Name	Descriptions and Applications	Details and Considerations
Transversus abdominis plane (TAP) block[71,833,834]	**Description:** Provides anesthesia to midline and lateral abdominal incisions. **Applicable Surgeries:** • Laparotomy • Laparoscopic hysterectomy[835,836] • Laparoscopic endometriosis surgery[837] • Cesarean delivery838 • Uterine myomectomy • Oophorectomy • Tubal ligation[839]	Injection of local anesthetic into the plane between the internal oblique and transversus abdominis muscles in the anterior or lateral abdominal wall. Although landmark-based approaches exist, this block is typically performed with ultrasound using a linear, high-frequency transducer. For the classic approach, coverage is most consistently reported from cutaneous dermatomes T10-L1 (umbilicus and below) and will provide unilateral analgesia to the skin, muscles and parietal peritoneum of the anterior abdominal wall. May be performed bilaterally but caution with total dose of local anesthetic. If more cephalad coverage is desired, consider rectus sheath and subcostal TAP blocks. Two randomized controlled trials have demonstrated that women receiving TAP blocks require less opioid in the first 24 hours after surgery, less nausea and vomiting, greater patient satisfaction and have longer times to rescue analgesia.[840,841] For obstetric procedures, the conventional TAP block is associated with significant technical difficulties and may risk peritoneal, hollow viscus and/or organ perforation. The TAP block can be introduced via an intra-abdominal approach, which is technically easier and also obviates the risks associated with the conventional TAP procedure.[838]

Appendix VI continued

Name	Descriptions and Applications	Details and Considerations
Quadratus lumborum (QL) blocks[842-846]	**Descriptions:** **QL1:** Anesthetizes the cutaneous branches of the iliohypogastric and ilioinguinal nerves as well as subcostal nerves T12-L1; for abdominal surgery below the umbilicus. **QL2:** T4-T12/L1 dermatomes; for any abdominal surgery. **Transmuscular QL block (TQL):** T4-T12/L1 dermatomes, so may be used for any abdominal surgery. Use bilateral QL blocks for midline incisions. **Applicable Surgeries:** • Exploratory laparotomy - Cesarean delivery[847-853]	Local anesthetic is deposited in the plane between the aponeurosis of the transversus abdominis muscle and the thoracolumbar fascia at a point just lateral to the quadratus lumborum muscle. Thus, needle entry is in the lateral or posterior abdominal wall. Local anesthetic injection occurs between the latissimus dorsi and quadratus lumborum muscles in the posterolateral abdominal wall. Approach is in the patient's flank, just above the iliac crest. Anesthetic is deposited in the fascial plane between the QL and the psoas major. Due to its location, this is considered an advanced block. When using QL block as the sole anesthetic for herniorrhaphy, instill the sac containing the peritoneum with local anesthetic to anesthetize the abdominal visceral nerves. QL block risks spread of local anesthetic to the paravertebral space. TQL blocks may result in lower extremity weakness.

Appendix VI continued

Name	Descriptions and Applications	Details and Considerations
Rectus sheath (RS) block[321,854,855]	**Description:** Anesthetizes the terminal branches of intercostal nerves 9-11, providing anesthesia over the midline anterior abdomen. **Applicable surgeries:** • Vertical midline or paramedian incisions • Midline laparotomy	Injection of local anesthetic deep to the rectus abdominis muscle and above the posterior rectus sheath. This sheath only extends along the upper two-thirds of the rectus abdominis muscle, stopping between the umbilicus and pubis. Thus, the block is performed at or above the level of the umbilicus on either side of midline and medial to the midclavicular line. Typically inject 10 mL per side. Up to one-third of patients may exhibit variations in anatomy, wherein the anterior cutaneous branch of the nerve courses superficial to the anterior wall of the rectus sheath. Because these nerves do not penetrate the posterior wall of the rectus sheath, these patients are at risk for incomplete block. RS block carries risk of puncture to inferior epigastric vessels.

Appendix VI continued

Name	Descriptions and Applications	Details and Considerations
Ilioinguinal and iliohypogastric (II-IH) nerve block[856-860]	**Description:** Anesthetizes the lower abdomen. **Applicable surgeries:** • Pfannenstiel incision • Cesarean delivery[861] • Chronic pelvic pain[862] • Endometriosis • Chronic postsurgical lower abdominal pain[862]	The II and IH nerves lie within the fascial plane between the internal oblique and transverse abdominis muscles at or above the level of the anterior superior iliac spine (TAP plane, but be aware that at this level, there are usually only two muscular layers clearly visible). These nerves may pierce the internal oblique muscle at or below the anterior superior iliac spine to travel within the plane between the external oblique aponeurosis and internal oblique muscle as they course inferomedially. There are often small vessels that course within the TAP plane with the II/IH nerves and may be useful for identification of the appropriate plane. Typically 10-20 mL of local anesthetic is injected into the plane with the nerves. When using II/IH block as the sole anesthetic for herniorrhaphy, instill the sac containing the peritoneum with local anesthetic to anesthetize the abdominal visceral nerves. II/IH nerve blocks risk blockade of the femoral nerve with incorrect needle placement and puncture of the inferior epigastric vessels.

Appendix VI continued

Name	Descriptions and Applications	Details and Considerations
Erector spinae plane (ESP) block[320,863-866]	**Description:** Local anesthetic spreads craniocaudal anterior to the erector spinae muscle and diffuses into the paravertebral spaces where it anesthetizes the dorsal and likely ventral ramus of the spinal nerve roots, and may spread laterally to anesthetize the intercostal nerves. **Applicable surgeries:** Used initially for thoracic surgery, however more recently used for abdominal surgery as well as surgery on the proximal lower extremities. May provide both visceral and somatic analgesia. Abdominal hysterectomy[867] Laparoscopic hysterectomy[868]	The injection is performed in the posterior thorax, where local anesthetic is deposited between the erector spinae muscle and the tip of the transverse process of the vertebrae (classically T5-T7, however case reports of use up to T2 and down to L4). Consider use of saline solution for hydrodissection, injecting anesthetic only after confirmation of proper placement of needle tip. While a linear ultrasound probe is adequate in most cases, consider using a curvilinear probe in obese patients and those with dense musculature. In theory dural puncture may be possible if the block is performed too medially and deeply.

Appendix VI continued

Name	Descriptions and Applications	Details and Considerations
Paravertebral nerve block (PVB)[869]	**Description:** PVB is in effect a unilateral block of the spinal nerve, including the dorsal and ventral rami, and sympathetic chain ganglion. While PVBs can be performed at any level, they are most frequently performed at the thoracic level due to anatomic considerations. **Applications:** • Bilateral blocks for midline abdominal surgery[870] • Major gynecologic surgery[871]	The thoracic paravertebral space is a wedge-shaped region adjacent to the spinal column, bound anteriorly by the parietal pleura, medially by the vertebral body, disc and intervertebral foramen and by the costotransverse ligament (a continuation of the innermost intercostal muscle) and transverse process posteriorly. For a single-level PVB, a total of 20-25 mL of long-acting local anesthetic is injected, whereas 4-5 mL is injected at each site for multi-level PVB. Consider the addition of epinephrine given the vascularity of the paravertebral space in order to delay systemic absorption. PVBs are unlikely to cause bleeding that results in an epidural hematoma, however they are subject to the same coagulation precautions as other neuraxial procedures. Contraindicated in empyema, malignant mass within the paravertebral space, patients in whom pneumothorax would not be tolerated. Unilateral PVBs may be considered as an alternative to TEA for patients in whom sympathectomy and subsequent hypotension is unlikely to be tolerated, however PVB does risk bilateral spread and thus bilateral sympathectomy. PVBs are contraindicated in patients with hypovolemia.

Technique: Description of each technique is beyond the scope of these guidelines. Many online resources can be found for education on regional anesthetic blocks. Provided below are reputable sites that may serve as a reference for anesthesiologists and surgeons.

Resources:

1. https://www.nysora.com
2. http://www.usra.ca/regional-anesthesia/specific-blocks/home.php
3. https://members.asra.com/pain-resource/regional-anesthesia/ (requires ASRA membership)
4. https://academic.oup.com/bjaed/article/10/6/182/299472
5. https://www.youtube.com/channel/UCV8d6B_W6KmPoL_bWXeYiqQ

Appendix VII

Primary and Adjunctive Pharmacologic Agents for Regional Anesthesia[872-874]

Primary Pharmacologic Agents for Regional Anesthesia

- It is recommended that amide anesthetic be a long-acting agent such as ropivacaine 0.5% or bupivacaine 0.5%. (Ropivacaine 0.2% and bupivacaine 0.25% are satisfactory alternatives in low body weight individuals.)
- Consider use of liposomal bupivacaine.
  - The manufacturer's site recommends injecting slowly, above and below fascial planes and into subcutaneous tissues using a 25-gauge or larger needle to maintain structural integrity of the liposomes. It is suggested that injections be 1-1.5 cm apart with 1-2 cc per injection site and can be mixed with 0.25% or 0.5% bupivacaine but NOT lidocaine.
  - There is also a volume expansion method involving dilution with normal saline up to 100 cc with 133 mg/10 cc vial.
  - See descriptions of amide anesthetics in "Nonopioid Pharmacologic Agents for Multimodal Analgesia" in **SECTION III, MULTIMODAL ANALGESIA IN OBSTETRIC AND GYNECOLOGIC PRACTICE**, for more information.
- Note: It is advised that clinicians exercise caution with use of amide anesthetics to avoid risk of LAST.
  - Total safe, cumulative dose of anesthetics will depend on patient-specific factors such as age, weight and liver function.
  - Generally, the limit on anesthetic administration is 4.5 mg/kg for lidocaine and 3 mg/kg for bupivacaine or ropivacaine.
  - Absorption of amide anesthetic varies greatly depending on route of administration. In order of greatest to least systemic absorption: IV, intercostal, caudal epidural, lumbar epidural, brachial plexus, IPLA, wound infiltration, subcutaneous.
- Note: Mixing of liposomal bupivacaine directly with lidocaine renders liposomal bupivacaine ineffective.
- It is recommended that a lipid rescue kit (i.e., lipid emulsion 20% infusion and appropriate dosing recommendations) be made readily available in any area of practice that utilizes amide anesthetic agents.

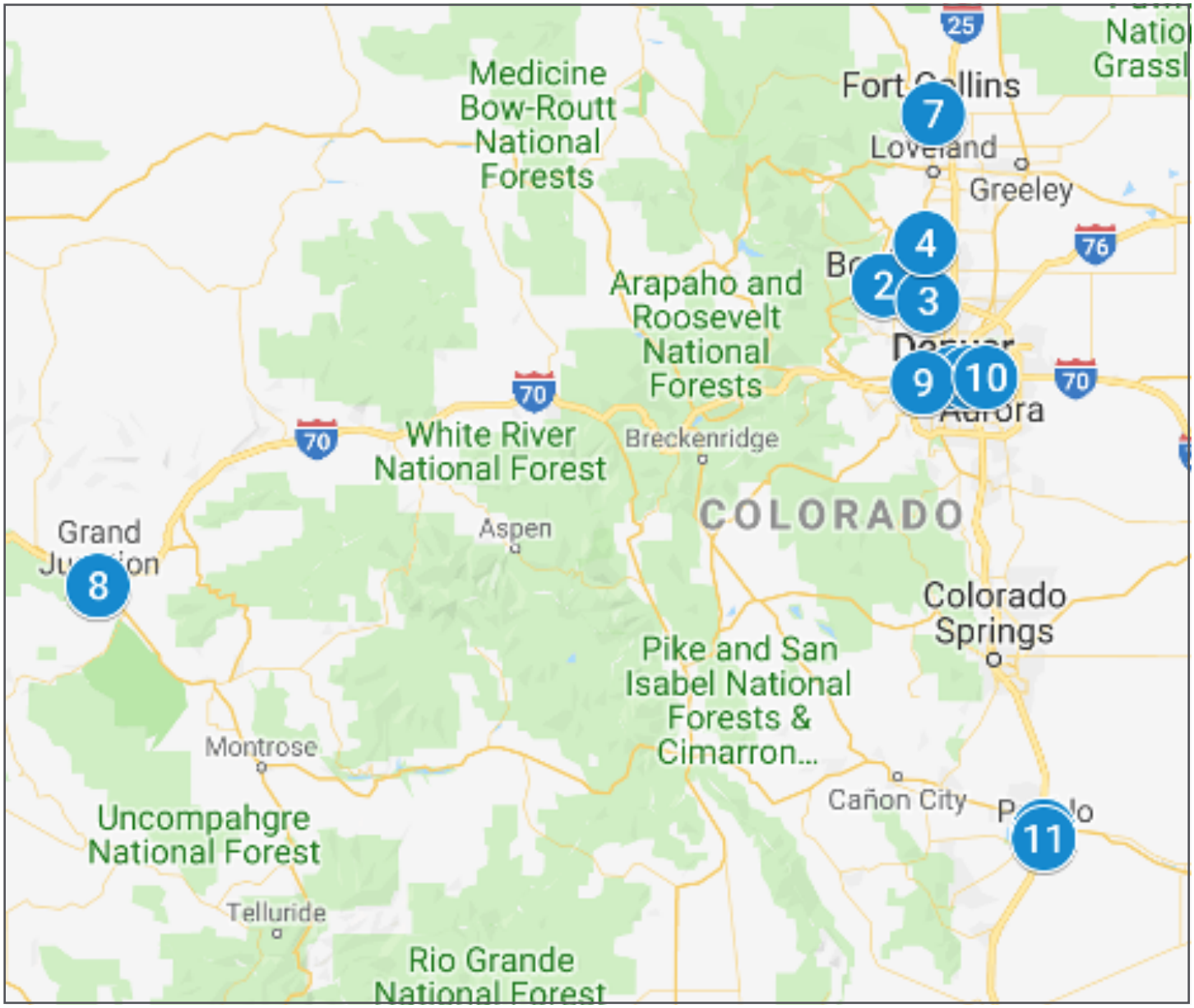
Adjunctive Pharmacologic Agents for Regional Anesthesia[872-874]

- Clonidine 0.5 mcg/kg; maximum dose of 150 mcg
- Epinephrine 5-10 mcg/mL
  - May extend duration of blocks via vasoconstrictive activity when used with lidocaine and mepivacaine (but not ropivacaine).
  - Cautions: Vasoconstriction may cause neuronal damage. Hypertension and tachycardia may signal the possibility of vascular injection.
- Dexamethasone: 5 mg per side[875-877]
- Dexmedetomidine: 20 mcg per side[878]

Appendix VIII

Map and Listing of Syringe Access Programs in Colorado

(updated March 2020)[879]



Appendix VIII continued

	Name	Address	Phone	Hours
1	Works Program – Boulder County Public Health	3482 Broadway Boulder, CO	303.413.7500	Mon - Fri 10:30am - 4:30pm
2	Works Program – Boulder County Public Health	29 Coffman, Ste. 200 Longmont, CO	303.678.6166	Mon - Fri 10:30am - 4:30pm
3	Works Program – Mental Health Partners	3180 Airport Road Boulder, CO	303.441.1281	After-hours, weekends, holidays
4	Works Program – Boulder County AIDS Project	2118 14th St. Boulder, CO	303.444.6121	Mon - Fri 2 - 5 pm
5	Works Program – Boulder County AIDS Project	Inside of Clinica Family Health 1735 S. Public Road Lafayette, CO	720.564.2708	Tuesdays and Thursdays 10:30am - 4:30pm
6	Access Point Denver	6260 E. Colfax Ave. Denver, CO	303.837.1501	Mon - Thurs 1 - 6pm Friday 12 - 3pm
7	Harm Reduction Action Center	231 E. Colfax Ave. Denver, CO	303.572.7800	Mon - Fri 9am - 12pm
8	Access Point Northern Colorado	400 Remington, Ste. 100 Fort Collins, CO	970.484.4469	Mon, Thurs 1 - 4:45pm Fri 9:30am - 4:45pm Tues 2 - 4:45pm Wed 1 - 6:45pm
9	Access Point Southern Colorado	807 N. Greenwood St., Ste. 200 Pueblo, CO	719.621.1105	Tue 10am - 12pm and 1:30 - 4pm
10	Points West	645 Parfet St. Lakewood, CO	303.239.7078	Mon - Fri 9am - 4pm
11	Aurora Syringe Access Services (ASAS)/Tri-County Health Department	Street outreach along Colfax Ave. Aurora, CO	303.363.3077	Mon, Tues, Thurs
12	ASAS/It Takes a Village	1475 Lima St. Aurora, CO	303.363.3077	Wed 1 - 3:30pm Street outreach: Tues, Thurs 1 - 3:30pm
13	Southern Colorado Harm Reduction Association	1249 E. Routt Ave. Pueblo, CO	719.289.7149	Sat 2 - 4pm
14	Vivent Health Lifepoint Program	Denver CO (mobile program)	720.385.6898	Mon - Fri 8am - 5pm

A complete list of local Colorado syringe access programs maintained by CDPHE can be found at (https://www.colorado.gov/pacific/cdphe/reducing-infections-injection-drug-use).

Appendix IX

Intimate Partner Violence Screening Questions[608]

NOTE: These sample screening questions have been adapted from the ACOG website

Obstetrician-gynecologists are encouraged to screen for IPV during new patient visits, annual examinations, initial prenatal visits, each trimester of pregnancy and the postpartum checkup, making sure to provide patient privacy.

Framing Statement:
"We've started talking to all of our patients about safe and healthy relationships, because it can have such a large impact on your health."

Confidentiality:
"Before we get started, I want you to know that everything here is confidential, meaning that I won't talk to anyone else about what is said unless you tell me that *[insert the laws in your state about what is necessary to disclose]."*

Sample Questions:
"Has your current partner ever threatened you or made you feel afraid?"
(Threatened to hurt you or your children if you did or did not do something, controlled who you talked to or where you went, or gone into rages.)

"Has your partner ever hit, choked or physically hurt you?"
("Hurt" includes being hit, slapped, kicked, bitten, pushed or shoved.)

For patients of reproductive age:
"Has your partner ever forced you to do something sexually that you did not want to do, or refused your request to use condoms?"

"Does your partner support your decision about when or if you want to become pregnant?"

"Has your partner ever tampered with your birth control or tried to get you pregnant when you didn't want to be?"

For patients with disabilities:
"Has your partner prevented you from using a wheelchair, cane, respirator or other assistive device?"
"Has your partner refused to help you with an important personal need such as taking your medicine, getting to the bathroom, getting out of bed, bathing, getting dressed or getting food or drink – or threatened not to help you with these personal needs?"

Appendix X

Urine Toxicology Screening[880]

DRUG	POSITIVE TEST	WINDOW OF DETECTION*	COMMENTS
Amphetamine; methamphetamine; 3,4-methylenedioxy-methamphetamine	Amphetamine	1–2 days	False positives with bupropion, chlorpromazine, desipramine, fuoxetine, labetalol, promethazine, ranitidine, pseudoephedrine, trazadone, and other common medications. Confrm unexpected positive results with the laboratory.
Barbiturates	Barbiturates	Up to 6 weeks	N/A
Benzodiazepines	Benzodiazepines	1–3 days; up to 6 weeks with heavy use of long-acting benzodiazepines	Immunoassays may not be sensitive to therapeutic doses, and most immunoassays have low sensitivity to clonazepam and lorazepam. Check with your laboratory regarding sensitivity and cutoffs. False positives with sertraline or oxaprozin.
Buprenorphine	Buprenorphine	3–4 days	Will screen negative on opiate screen. Tramadol can cause false positives. Can be tested for specifcally.
Cocaine	Cocaine, benzoylecgonine	2–4 days; 10–22 days with heavy use	N/A
Codeine	Morphine, codeine, high-dose hydrocodone	1–2 days	Will screen positive on opiate immunoassay.
Fentanyl	Fentanyl	1–2 days	Will screen negative on opiate screen. Can be tested for specifcally. May not detect all fentanyl-like substances.
Heroin	Morphine, codeine	1–2 days	Will screen positive on opiate immunoassay. 6-monoacetylmorphine, a unique metabolite of heroin, is present in urine for about 6 hours. Can be tested for specifcally to distinguish morphine from heroin, but this is rarely clinically useful.
Hydrocodone	Hydrocodone, hydromorphone	2 days	May screen negative on opiate immunoassay. Can be tested for specifcally.
Hydromorphone	May not be detected	1–2 days	May screen negative on opiate immunoassay. Can be tested for specifcally.
Marijuana	Tetrahydrocannabinol	Infrequent use of 1–3 days; chronic use of up to 30 days	False positives possible with efavirenz, ibuprofen, and pantoprazole.

**Detection time may vary depending on the cutoff.*

Continued

Appendix X continued

DRUG	POSITIVE TEST	WINDOW OF DETECTION*	COMMENTS
Methadone	Methadone	2–11 days	Will screen negative on opiate screen. Can be tested for specifcally.
Morphine	Morphine, hydromorphone	1–2 days	Will screen positive on opiate immunoassay. Ingestion of poppy plant/seed may screen positive.
Oxycodone	Oxymorphone	1–1.5 days	Typically screens negative on opiate immunoassay. Can be tested for specifcally.

**Detection time may vary depending on the cutoff.*

Appendix XI

Characteristics of Medications Used for Addiction Treatment

Characteristic	Methadone	Buprenorphine	Naltrexone
Brand names	Dolophine, Methadose	Subutex, Suboxone, Zubsolv, Sublocade, Probuphine	Depade, ReVia, Vivitrol
Opioid receptor effect	Agonist	Partial agonist	Antagonist
Route of Administration	Oral	Sublingual, buccal, subdermal implant, subcutaneous extended release injection	Oral, intramuscular extended-release
Regulations and availability	Schedule II; only available at federally certified OTPs and the acute inpatient hospital setting	Schedule III; requires waiver to prescribe outside OTPs Implant: Prescribers must be certified in the Probuphine Risk Evaluation and Mitigation Strategy (REMS) Program. Providers who wish to insert/remove implants are required to obtain special training and certification in the REMS Program. Subcutaneous injection: Health care settings and pharmacies must be certified in the Sublocade REMS Program	Not a scheduled medication; not included in OTP regulations; requires prescription; available at office-based treatment or specialty substance use treatment programs, including OTPs
Frequency of dosing	Taken once per day orally	Taken orally or sublingually usually once a day; or available in an implantable device	Taken once a day orally or by injection once a month
Caution or avoid	Allergy, severe hepatic disease, QTc prolongation, drug interactions, high-risk employment	Allergy, severe liver disease, heavy EtOH or BZD use, recent methadone	Allergy, use of prescription or nonmedical opioids in prior week, hepatic disease, hepatitis, renal impairment, depression or suicidal ideation
Risk of withdrawal when starting medication	None	Risk of precipitated withdrawal	Risk of precipitated withdrawal if opioid exposure in previous 7-10 days

Continued

Appendix XI continued

Characteristic	Methadone	Buprenorphine	Naltrexone
Adverse effects	QT prolongation, torsades de pointes, constipation, hyperhidrosis, respiratory, depression, sedation, sexual dysfunction, hypogonadism, orthostatic hypotension and syncope, misuse/diversion potential, neonatal opioid withdrawal syndrome	Constipation, nausea, headache, insomnia, hyperhidrosis, peripheral edema, respiratory depression (particularly combined with benzodiazepines or other CNS depressants), misuse/diversion potential, neonatal opioid withdrawal syndrome Implant: Nerve damage during insertion/removal, accidental overdose or misuse if extruded, local migration or protrusion Subcutaneous injection: Injection site itching or pain, death from IV injection	Nausea, headache, diarrhea, anxiety, insomnia, depression, suicidality, myalgia, arthralgia, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders Intramuscular: Pain, swelling, induration (including some cases requiring surgical intervention)
Sedation, respiratory depression and/or overdose risk	Moderate. At high doses in nontolerant patients or slow metabolizers has potential for sedation, respiratory depression and/or death. Concurrent use of sedating drugs, e.g., other opioids, alcohol/ benzodiazepines, increases risk of poisoning. Risk of overdose is higher when initiating treatment.	Low. Ceiling effect for respiratory depression, therefore lower risk of respiratory depression and/or death. Concurrent use of sedating drugs, e.g., other opioids, alcohol/ benzodiazepines, increases risk of poisoning.	None. Increased sensitivity to opioids after use and higher risk of overdose with relapse to opioid use.
Visit frequency	Daily visits to maintenance treatment program, take-homes may be allowed if stable for long term. This structure helps some patients, some dislike it.	Can range from daily to monthly depending on patient treatment needs, may be provided in primary care setting. Also available in some methadone clinics, increasing structure and decreasing diversion risk.	As determined by clinician. Monthly depot needs visit to clinic or pharmacist.
Diversion potential	Low for directly observed therapy (DOT), high for take-home	Low for DOT, moderate for take-homes, reduced by coformulation with naloxone	None
Who can prescribe after discharge?	Opioid treatment program (OTP) only	Any physician, NP or PA who has been trained and possesses DATA2000 waivers (aka “X-number”)	Naltrexone can be prescribed by any health care clinician who is licensed to prescribe medications

Continued

Appendix XI continued

Characteristic	Methadone	Buprenorphine	Naltrexone
Advantages	Long history of safety and efficacy. Highest treatment retention.	Safe and effective. Can be prescribed by certified clinician in an office-based opioid treatment (OBOT), which eliminates the need to visit specialized treatment clinics and thus widens availability.	Does not induce dependence or sedation; a recently approved depot injection formulation, Vivitrol, eliminates need for daily dosing.
Disadvantages	Requires daily visit to OTP	Requires withdrawal symptoms prior to initiation. Subutex has measurable misuse and diversion liability; Suboxone diminishes this risk by including naloxone, an antagonist that induces withdrawal if the drug is injected but is not bioavailable if taken as directed.	Poor patient compliance. Initiation requires a 7-10 day opioid-free interval, during which withdrawal, relapse and treatment dropout may occur.
Retention in treatment	Higher in methadone, possibly as consequence of the increased structure of OTP	May be slightly lower than methadone, retention improves at doses over 16 mg	Naltrexone was found to have better 3-, 6- or 12-month retention rates than patients who received a placebo or no medication, but evidence of naltrexone's long-term efficacy has not been strongly established.
Mortality	Methadone substantially decreases all-cause mortality compared to no treatment.	Buprenorphine substantially decreases all-cause mortality compared to no treatment.	The mortality rate for naltrexone was four times higher than for methadone when calculated as deaths per number of episodes of treatment and substantially higher than for buprenorphine.

SOURCES: adapted from:
Medication-Assisted Therapies – Tackling the Opioid-Overdoes Epidemic. Volkow, M.D.[881]
Medications for Opioid Use Disorder. SAMHSA TIP 63[880]
Project SHOUT – Inpatient Management of Opioid Use Disorder: Buprenorphine[882]
Mortality risk during and after opioid substitution treatment[883]
Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial[884]
Retention in MAT for opiate dependence: A systematic review[885]
Mortality related to naltrexone in the treatment of opioid dependence[886]
Naltrexone. SAMHSA[887]

Appendix XII

Patient-Centered Decision Considerations when Selecting an Opioid Agonist Medication for a Pregnant Patient[651]

Considerations	Buprenorphine	Methadone
Patient Selection	May be preferable for patients who are new to treatment because it is easier to transfer from buprenorphine to methadone (it can be very difficult to transfer from methadone to buprenorphine), who do not like or want methadone, or who have requested this medication.	May be preferable for patients who do not like or want buprenorphine treatment or who have requested this medication.
Care	Includes a prenatal healthcare professional, parenting classes, and SUD treatment.	Includes a prenatal healthcare professional, parenting classes, and SUD treatment.
Dispensing	May be prescribed in an office setting with weekly or biweekly prescribing/dispensing or provided in an opioid treatment program.	Requires daily visits to a federally certified opioid treatment program; take-home medication is provided for patients meeting specific requirements.
Treatment Retention	Some studies show treatment dropout is higher than that for methadone.	Some studies show treatment retention is higher than that for buprenorphine.
Risk of Medication Interaction	Few known interactions with other medications; risk of interaction is greatest with central nervous system (CNS) depressants and CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, atazanavir). If these medications must be used, the clinic should monitor the patient daily for increased effect of buprenorphine; healthcare professionals should be aware that the development of sign and symptom varies and depends on a variety of factors. Other agonist/antagonist medications (e.g., butorphanol, dezocine, nalbuphine, pentazocine) and full antagonists will result in precipitated withdrawal.	Medications that use CYP450 enzymes are commonly involved in a methadone-medication interaction. Methadone is metabolized primarily by CYP3A4 and CYP2B6. There is evidence that other CYP450 enzymes are also involved including CYP2D6. Known interactions with other medications in pregnant women are detailed in McCance-Katz (2011). If these medications must be used, the clinic should monitor the patient daily for increased or decreased effect of methadone; healthcare professionals should be aware that the development of sign and symptom varies and depends on a variety of factors. Other agonist/antagonist medications (e.g., butorphanol, dezocine, nalbuphine, pentazocine) and full antagonists will result in precipitated withdrawal.
Starting Dose	2–4 mg	20–30 mg
Target Dose	Daily, 16 mg or product equivalent to 16 mg, is the most common dosage. The optimal dose will be determined by regular assessment of the individual and her response to treatment.	Daily, 80–120 mg. The optimal dose will be determined by regular assessment of the individual and her response to treatment.
Interval at Which Dose May Be Increased	Daily, but dose changes should not be made without patient assessment.	3 days is a common interval in a clinical practice, but dose changes should not be made without patient assessment.

Continued

Appendix XII continued

Considerations	Buprenorphine	Methadone
Risk of Overdose and Death	Generally lower risk compared with full opioid agonists; overdose is possible when combined with other CNS depressants. Continued buprenorphine treatment reduces mortality after release from incarceration (Degenhardt et al., 2014). Buprenorphine treatment reduces the risk of death in people dependent on opioids (Gibson et al., 2008) and drug-related mortality in the first 4 weeks of treatment, a high-risk period (Kimber, Larney, Hickman, Randall & Degenhardt, 2015).	Generally greater risk of overdose compared with mixed agonist/antagonist opioids; overdose is possible when combined with other CNS depressants. Continued methadone treatment reduces mortality after release from incarceration (Degenhardt et al., 2014). Methadone significantly reduces the risk of drug-related mortality compared with no treatment (Evans et al., 2015). Methadone treatment reduces the risk of death in people dependent on opioids (Gibson et al., 2008) and drug-related mortality in the first 4 weeks of treatment, a high-risk period (Kimber et al., 2015).
Risk of Sedation	Sedation is possible but typically milder than that with full μ opioid agonists.	Sedation is possible and may be greater than that with partial agonist opioids (Walsh, Preston, Bigelow, & Stitzer, 1995).
Ability To Fill a Prescription at a Local Pharmacy	Is possible depending on pharmacy availability.	Can be filled in a certified pharmacy to treat pain, but methadone for the treatment of OUD cannot generally be obtained from a pharmacy in the United States. It must be administered or dispensed for treatment of OUD at a certified opioid treatment program.
Treatment in a Healthcare Professional's Office	Healthcare professionals who request a waiver to prescribe buprenorphine from SAMHSA and receive a unique Drug Enforcement Administration registration number for this purpose may prescribe buprenorphine for the treatment of opioid use disorder in an office-based setting.	May be possible under federal regulation if specific program criteria are fulfilled and relevant state and federal permission is sought.
Risk of NAS	Approximately 50% of exposed neonates are treated for NAS; NAS may be milder with buprenorphine compared with full mu opioid agonists such as most opioid analgesics and methadone.	Approximately 50% of exposed neonates are treated for NAS.
Time to NAS Onset	American Academy of Pediatrics (AAP) recommends monitoring prenatally opioid-exposed neonates for a minimum of 4–7 days after delivery (Hudak, Tan, & AAP, 2012).	AAP recommends monitoring prenatally opioid-exposed neonates for a minimum of 4–7 days after delivery (Hudak, Tan, & AAP, 2012).

Continued

Appendix XII continued

Considerations	Buprenorphine	Methadone
Duration of NAS	Most studies show shorter NAS duration compared with methadone.	Most studies show longer NAS duration compared with buprenorphine.
Breastfeeding Considerations	Generally safe if the mother is stable and the ABM Clinical Protocol #21 breastfeeding with SUD guidelines are met.	Generally safe if the mother is stable and the ABM Clinical Protocol #21 breastfeeding with SUD guidelines are met.
Neurodevelopmental Outcomes of Exposed Children	Available research suggests there is not a linear cause and effect relationship between prenatal buprenorphine exposure and developmental problems when compared with other opioids; the research base is limited.	Available research suggests there is not a linear cause and effect relationship between prenatal methadone exposure and developmental problems when compared with other opioids; the research base is limited.

Continued

Appendix XIII

Quick Start Guide for Methadone[888]

CA BRIDGE
TREATMENT STARTS HERE

Methadone Hospital Quick Start*

Opioid Use Disoder (OUD) & ready to start methadone treatment

YES

If no sedation give 10-30mg methadone

4 hours

Continued withdrawals/cravings?

YES

If no sedation give 5-10mg methadone

q4 hours

Day 1: Max dose 40mg

DAYS 2 AND 3

If no sedation give total dose from prior 24 hours

4 hours

Continued withdrawals/cravings?

YES

If Ramsay ≤2 give 5-10mg methadone

q4 hours

Day 2: Max 50mg

Day 3: Max 60mg

After initial 72 hours: cont same dose for 5 days, can increase dose by 10mg q5days

DISCHARGE

- Methadone may not be prescribed for OUD. Must be administered in a methadone clinic
- **Naloxone 4mg/0.1ml**

***Quick start is for people not already on methadone for OUD. If a patient is already in a methadone maintenance program:**

- Confirm maintenance dose, give maintenance dose.
- If unable to confirm dose, give methadone 30-40mg and increase to full dose when dose is confirmed. OK to uptitrate per protocol until dose confirmed.
- If patient missed outpatient dosing, strongly recommended to discuss dosing changes with methadone clinic provider.
  - If patient missed dose and dose is confirmed by clinic but clinic provider cannot be reached:
  - If 1-2 days are missed, give patient's regular dose
  - If 3-4 days are missed, give half patient's regular dose
  - If ≥5 days are missed, treat as a new start.

Emergency Department

- May provide methadone up to 72 hours pending linkage. Confirm dose whenever possible.
- If unable to confirm dose, OK to provide methadone 30mg/day.
- Patients may need bridge dose if recent hospitalization, prison or jail discharge, or if they missed a dose at their methadone clinic.

Ramsay sedation score

Some hospitals may define no sedation as Ramsay ≤2

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

Complicating Factors

- Allergy to methadone
- Respiratory depression
- Ramsay sedation scale ≥3
- QTc ≥500
- Recent use of benzodiazepines, alcohol or other sedatives
- Severe liver disease
- Medically unstable
- If RR <8 or sedated, do not give additional methadone

Initial Dosing

- Patients should be dosed according to tolerance. May use morphine equivalent calculator as a guide. Withdrawal severity is not well correlated with tolerance.
- Can use adjunctive medications for withdrawal symptoms.
- Order naloxone prn sedation/resp depression.

Pregnancy

Methadone is safe in pregnancy and in breastfeeding.

NOVEMBER 2019

Appendix XIV

Buprenorphine Quick Start Guide in Pregnancy[882]

ColoradoMAT

Buprenorphine (Bup) Quick Start in Pregnancy

- Bup is a high-affinity partial agonist opioid that is SAFE in pregnancy and highly effective for treating opioid use disorder.
- If patient is stable on methadone or prefers methadone, recommend continuation of methadone as first-line treatment.
- Fetal Monitoring is not required to start Bup in a normal pregnancy regardless of gestational age.
- Admission for observation is NOT required at Bup starts.
- Bup/Nx or Bup monoproduct is OK in Pregnancy.
- Split dosing and an increase in total Bup dose is often necessary esp in later trimesters.

Uncomplicated* opioid withdrawal?**

NO → **Start Bup after withdrawal**
Supportive meds prn, stop other opioids

YES (stop other opioids)

Administer 8mg Bup SL

(one hour)

Withdrawal symptoms improved?

NO → **No Improvement**
Differential Diagnosis:
- **Withdrawal mimic:** Pre-eclampsia, benzo withdrawal, influenza, DKA, sepsis, thyrotoxicosis, etc. Treat underlying illness.
- **Incompletely treated withdrawal:** Occurs with lower starting doses, improves with more Bup.
- **Bup side-effect:** Nausea, headache, dysphoria. Continue Bup, treat symptoms with supportive medications.
- **Precipitated withdrawal:** Too large a dose started too soon after opioid agonist. Severe withdrawal is dangerous for pregnancy, and you should consult Rocky Mountain Poison Control. Usually time limited, self resolving with supportive medications.

YES

Administer 2nd dose
ED: 8-24mg; consider higher loading dose for longer effect on discharge
Inpatient: 8mg; On subsequent days, titrate from 8mg BID with additional 4-8mg prn cravings

Maintenance Treatment
16 mg Bup SL/day
Usual total daily dose Bup SL 16-32mg; Titrate to suppress cravings

Discharge
- Document Opioid Withdrawal and/or Opioid Use Disorder as a diagnosis.
- **If no X-waiver:** Use loading dose up to 32mg for long effect and give rapid follow up.
- **If X-waiver:** Prescribe sufficient Bup/Nx until follow-up. Consider bridging dose of 16mg/day.

Overdose Education
Naloxone Kit
Naloxone 4mg/0.1ml intranasal spray

PROVIDER RESOURCES:

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

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

Peripartum

For planned C-Section and/or labor, or acute pain:
- Continue patient's normal Bup dose in combination with multimodal analgesia that may include regional anesthesia and opioids.
- Bup is safe for breastfeeding.
- Bup reduces NAS severity. Dose does not correlate to NAS severity.
- Postpartum Bup dose reduction should be gradual and per pt cravings.

Buprenorphine Dosing

- Any provider can order Bup in the ED or inpatient.
- If unable to take SL, try Bup 0.3mg IV/IM.
- Total initial daily dose above 16mg may increase duration of action beyond 24 hrs.
- Ok to start with lower initial dose: Bup 2-4mg SL

* Complicating Factors

- Severe acute pain or trauma
- Significant respiratory compromise, medically unstable (do not start Bup)
- Recent methadone

** Diagnosing Opioid Withdrawal

Subjective symptoms AND one objective sign

Subjective symptons:
- Patient reports feeling "bad" due to withdrawal (nausea, stomach cramps, body aches, restlessness, hot and cold, stuffy nose).

Objective signs [at least one]:
- Restlessness, sweating, rhinorrhea, dilated pupils, watery eyes, tachycardia, yawning, goose bumps, vomiting, diarrhea, tremor.

Typical withdrawal onset:
- ≥12 hrs after short acting opioid
- ≥24 hrs after long acting opioid
- ≥48 hrs after methadone (can be >72 hrs)

If unsure, use COWS (clinical opioid withdrawal scale).
Start if COWS ≥ 8 AND one objective sign.

If Completed Withdrawal
Typically >72 hrs since last short-acting opioid, may be longer for methadone. Start Bup 4mg q4h prn cravings, usual dose 16-32mg/day. Subsequent days, usual dosing frequency TID or QID

Symptomatic / Supportive Meds

Can be used to help treat withdrawal symptoms prn or during induction process (i.e. clonidine, acetaminophen, ondansetron, diphenhydramine, etc).

Adapted from California Bridge, a program of the Public Health Institute (www.bridgetotreatment.org)

c|h|a Colorado Hospital Association

References

1 Centers for Disease Control and Prevention. Ten Leading Causes of Death and Injury. Published April 10, 2019. Accessed September 12, 2019. https://www.cdc.gov/injury/wisqars/LeadingCauses

2 Scholl L. Drug and Opioid-Involved Overdose Deaths — United States, 2013–2017. MMWR Morb Mortal Wkly Rep. 2019;67. doi:10.15585/mmwr.mm6751521e1

3 Centers for Disease Control and Prevention. Understanding the Epidemic. Published July 24, 2019. Accessed July 24, 2019. https://www.cdc.gov/drugoverdose/epidemic/index.html

4 Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States.Surveillance Special Report. Published August 31, 2018. Accessed September 12, 2019. https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf

5 Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in Medical Use and Abuse of Opioid Analgesics. JAMA. 2000;283(13):1710-1714. doi:10.1001/jama.283.13.1710

6 Centers for Disease Control and Prevention. Prescription Opioid Data. Published July 11, 2019. Accessed September 12, 2019. https://www.cdc.gov/drugoverdose/data/prescribing.html

7 Substance Abuse and Mental Health Services Administration. The TEDS Report: Length of Time from First Use to Adult Treatment Admission. Published September 29, 2011. Accessed September 12, 2019. https://www.datafiles.samhsa.gov/study-publication/length-time-first-use-adult-treatment-admission-nid15982

8 Hedegaard H. Drug Overdose Deaths in the United States, 1999–2016. 2017;(294):8.

9 Substance Abuse and Mental Health Services Administration. Treatment Episode Data Set (TEDS): 2017 Admissions to and Discharges from Publicly-Funded Substance Use Treatment. Published May 15, 2019. Accessed September 12, 2019. https://www.samhsa.gov/data/report/treatment-episode-data-set-teds-2017-admissions-and-discharges-publicly-funded-substance-use

10 White House Council of Economic Advisers. The Full Cost of the Opioid Crisis: $2.5 Trillion Over Four Years. Published October 28, 2019. https://www.whitehouse.gov/articles/full-cost-opioid-crisis-2-5-trillion-four-years/

11 Wilkerson R, Kim H, Windsor T, Mareiniss D. The Opioid Epidemic in the United States. Emerg Med Clin North Am. 2016;34(2):e1-e23. doi:10.1016/j.emc.2015.11.002

12 Catan T, Perez E. A Pain-Drug Champion Has Second Thoughts. The Wall Street Journal. http://www.wsj.com/articles/SB10001424127887324478304578173342657044604. Published 2012. Accessed September 12, 2019.

13 Von Korff M, Kolodny A, Deyo RA, Chou R. Long-Term Opioid Therapy Reconsidered. Ann Intern Med. 2011;155(5):325. doi:10.7326/0003-4819-155-5-201109060-00011

14 Grady D, Berkowitz SA, Katz MH. Opioids for chronic pain. Arch Intern Med. 2011;171(16):1426-1427. doi:10.1001/archinternmed.2011.213

15 Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. BMJ. 2011;343:d5142. doi:10.1136/bmj.d5142

16 American Academy of Pain Medicine. Use of Opioids for the Treatment of Chronic Pain. Published March 7, 2013. Accessed September 12, 2019. https://painmed.org/about/position-statements/use-of-opioids-for-the-treatment-of-chronic-pain

17 Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surg. 2017;152(6):e170504. doi:10.1001/jamasurg.2017.0504

18 Lanser P, Gesell S. Pain management: the fifth vital sign. Healthc Benchmarks. 2001;8(6):68-70, 62.

19 Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. National Academies Press (US); 2011. Accessed February 12, 2020. http://www.ncbi.nlm.nih.gov/books/NBK91497/

20 Bhakta HC, Marco CA. Pain Management: Association with Patient Satisfaction among Emergency Department Patients. J Emerg Med. 2014;46(4):456-464. doi:10.1016/j.jemermed.2013.04.018

21 Colorado Department of Public Health and Environment. Drug overdose deaths in Colorado, 2000-2018. Published 2019. Accessed August 18, 2019. https://www.colorado.gov/pacific/cdphe

22 Colorado Department of Public Health and Environment, Violence and Injury Prevention-Mental Health Promotion Branch, Opioid Overdose Prevention Unit. Colorado Opioid Profile. Published 2018. Accessed August 18, 2019. https://www.colorado.gov/pacific/cdphe/prescription-drug-data-profiles

23 Colorado Health Institute. New data from the Colorado Department of Public Health and Environment (CDPHE) show that 974 Coloradans died of drug overdoses in 2018 — the second highest total on record behind the 1,012 deaths recorded in 2017. Published 2019. Accessed February 12, 2020. https://www.coloradohealthinstitute.org/research/more-coloradans-died-meth-overdoses-2018-ever

24 Centers for Disease Control and Prevention. Multiple Cause of Death, 1999-2018 on CDC WONDER Online Database. National Center for Health Statistics. Published February 14, 2018. Accessed July 27, 2020. https://wonder.cdc.gov/mcd-icd10.html

25 Colorado Consortium for Prescription Drug Abuse Prevention, OMNI Institute. Consortium Dashboard. Published March 4, 2019. Accessed September 12, 2019. https://public.tableau.com/profile/omni#!/vizhome/RXConsortiumdashboard/Readmefirst

26 Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. J Pain Off J Am Pain Soc. 2015;16(8):769-780. doi:10.1016/j.jpain.2015.05.002

27 CDC. Prescription Painkiller Overdoses. Centers for Disease Control and Prevention. Published September 4, 2018. Accessed July 27, 2020. https://www.cdc.gov/vitalsigns/prescriptionpainkilleroverdoses/index.html

References continued

28 Centers for Disease Control and Prevention. Vital Signs: Prescription Painkiller Overdoses. Published September 4, 2018. https://www.cdc.gov/vitalsigns/prescriptionpainkilleroverdoses/index.html

29 National Institute on Drug Abuse. Substance Use in Women DrugFacts. DrugAbuse. Published January 2020. https://www.drugabuse.gov/publications/drugfacts/substance-use-in-women

30 Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. MMWR Morb Mortal Wkly Rep. 2017;66(10):265-269. doi:10.15585/mmwr.mm6610a1

31 Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term Analgesic Use After Low-Risk Surgery: A Retrospective Cohort Study. Arch Intern Med. 2012;172(5):425-430. doi:10.1001/archinternmed.2011.1827

32 Carroll I, Barelka P, Wang CKM, et al. A pilot cohort study of the determinants of longitudinal opioid use after surgery. Anesth Analg. 2012;115(3):694-702. doi:10.1213/ANE.0b013e31825c049f

33 Swenson CW, Kamdar NS, Seiler K, Morgan DM, Lin P, As-Sanie S. Definition development and prevalence of new persistent opioid use following hysterectomy. Am J Obstet Gynecol. 2018;219(5):486.e1-486.e7. doi:10.1016/j.ajog.2018.06.010

34 Bateman BT, Cole NM, Maeda A, et al. Patterns of Opioid Prescription and Use After Cesarean Delivery. Obstet Gynecol. 2017;130(1):29-35. doi:10.1097/AOG.0000000000002093

35 Peahl AF, Dalton VK, Montgomery JR, Lai Y-L, Hu HM, Waljee JF. Rates of New Persistent Opioid Use After Vaginal or Cesarean Birth Among US Women. JAMA Netw Open. 2019;2(7). doi:10.1001/jamanetworkopen.2019.7863

36 Madsen AM, Stark LM, Has P, Emerson JB, Schulkin J, Matteson KA. Opioid Knowledge and Prescribing Practices Among Obstetrician-Gynecologists. Obstet Gynecol. 2018;131(1):150-157. doi:10.1097/AOG.0000000000002407

37 As-Sanie S, Till SR, Mowers EL, et al. Opioid Prescribing Patterns, Patient Use, and Postoperative Pain After Benign Hysterectomy. Obstet Gynecol. 2017;130(6):1261-1268. doi:10.1097/AOG.0000000000002344

38 Movilla PR, Kokroko JA, Kotlyar AG, Rowen TS. Postoperative Opioid Use Using Enhanced Recovery After Surgery Guidelines for Benign Gynecologic Procedures. J Minim Invasive Gynecol. 2020;27(2):510-517. doi:10.1016/j.jmig.2019.04.017

39 Patanwala I, Ouyang C, Fisk M, Lamvu G. Opioid Prescription Usage after Benign Gynecologic Surgery: A Prospective Cohort Study. J Minim Invasive Gynecol. 2020;27(4):860-867. doi:10.1016/j.jmig.2019.07.007

40 Badreldin N, Grobman WA, Chang KT, Yee LM. Opioid prescribing patterns among postpartum women. Am J Obstet Gynecol. 2018;219(1):103.e1-103.e8. doi:10.1016/j.ajog.2018.04.003

41 Osmundson SS, Schornack LA, Grasch JL, Zuckerwise LC, Young JL, Richardson MG. Postdischarge Opioid Use After Cesarean Delivery. Obstet Gynecol. 2017;130(1):36-41. doi:10.1097/AOG.0000000000002095

42 Bartels K, Mayes LM, Dingmann C, Bullard KJ, Hopfer CJ, Binswanger IA. Opioid Use and Storage Patterns by Patients after Hospital Discharge following Surgery. Costigan M, ed. PLOS ONE. 2016;11(1):e0147972. doi:10.1371/journal.pone.0147972

43 Prabhu M, Garry EM, Hernandez-Diaz S, MacDonald SC, Huybrechts KF, Bateman BT. Frequency of Opioid Dispensing After Vaginal Delivery. Obstet Gynecol. 2018;132(2):459-465. doi:10.1097/AOG.0000000000002741

44 Mark J, Argentieri DM, Gutierrez CA, et al. Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. JAMA Netw Open. 2018;1(8):e185452. doi:10.1001/jamanetworkopen.2018.5452

45 Bicket MC, Long JJ, Pronovost PJ, Alexander GC, Wu CL. Prescription Opioid Analgesics Commonly Unused After Surgery: A Systematic Review. JAMA Surg. 2017;152(11):1066-1071. doi:10.1001/jamasurg.2017.0831

46 Williams JT, Ingram SL, Henderson G, et al. Regulation of μ-Opioid Receptors: Desensitization, Phosphorylation, Internalization, and Tolerance. Pharmacol Rev. 2013;65(1):223-254. doi:10.1124/pr.112.005942

47 Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia—when is enough too much? A review of opioid-induced tolerance and hyperalgesia. The Lancet. 2019;393(10180):1558-1568. doi:10.1016/S0140-6736(19)30430-1

48 Møller LF, Matic S, van den Bergh BJ, Moloney K, Hayton P, Gatherer A. Acute drug-related mortality of people recently released from prisons. Public Health. 2010;124(11):637-639. doi:10.1016/j.puhe.2010.08.012

49 Buster MCA, Brussel GHA van, Brink W van den. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. Addiction. 2002;97(8):993-1001. doi:10.1046/j.1360-0443.2002.00179.x

50 de Leon-Casasola OA. Opioids for Chronic Pain: New Evidence, New Strategies, Safe Prescribing. Am J Med. 2013;126(3, Supplement 1):S3-S11. doi:10.1016/j.amjmed.2012.11.011

51 The Colorado Opioid Safety Collaborative. 2017 Colorado Opioid Safety Pilot Results Report. Published online May 2018. Accessed September 12, 2019. https://cha.com/wp-content/uploads/2018/06/CHA-Opioid-Pilot-Results-Report-May-2018.pdf

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

53 Liang X, Liu R, Chen C, Ji F, Li T. Opioid System Modulates the Immune Function: A Review. Transl Perioper Pain Med. 2016;1(1):5-13.

54 Afsharimani B, Cabot P, Parat M-O. Morphine and tumor growth and metastasis. Cancer Metastasis Rev. 2011;30(2):225-238. doi:10.1007/s10555-011-9285-0

55 Tuerxun H, Cui J. The dual effect of morphine on tumor development. Clin Transl Oncol. 2019;21(6):695-701. doi:10.1007/s12094-018-1974-5

56 Cata JP, Keerty V, Keerty D, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. Cancer Med. 2014;3(4):900-908. doi:10.1002/cam4.236

57 Zhang XY, Liang YX, Yan Y, Dai Z, Chu HC. Morphine: double-faced roles in the regulation of tumor development. Clin Transl Oncol. 2018;20(7):808-814. doi:10.1007/s12094-017-1796-x

References continued

58 Gach K, Wyrębska A, Fichna J, Janecka A. The role of morphine in regulation of cancer cell growth. Naunyn Schmiedebergs Arch Pharmacol. 2011;384(3):221. doi:10.1007/s00210-011-0672-4

59 Meserve JR, Kaye AD, Prabhakar A, Urman RD. The role of analgesics in cancer propagation. Best Pract Res Clin Anaesthesiol. 2014;28(2):139-151. doi:10.1016/j.bpa.2014.04.004

60 Zylla D, Kuskowski MA, Gupta K, Gupta P. Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer. BJA Br J Anaesth. 2014;113(suppl_1):i109-i116. doi:10.1093/bja/aeu351

61 Lennon FE, Mirzapoiazova T, Mambetsariev B, et al. The Mu Opioid Receptor Promotes Opioid and Growth Factor-Induced Proliferation, Migration and Epithelial Mesenchymal Transition (EMT) in Human Lung Cancer. PLoS ONE. 2014;9(3). doi:10.1371/journal.pone.0091577

62 Kaye AD, Patel N, Bueno FR, et al. Effect of Opiates, Anesthetic Techniques, and Other Perioperative Factors on Surgical Cancer Patients. Ochsner J. 2014;14(2):216-228.

63 Patvardhan C, Ferrante M. Opiate free anaesthesia and future of thoracic surgery anaesthesia. J Vis Surg. 2018;4(0). Accessed February 13, 2020. http://jovs.amegroups.com/article/view/23071

64 Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. BJA Br J Anaesth. 2014;112(6):991-1004. doi:10.1093/bja/aeu137

65 Ramaswamy S, Wilson JA, Colvin L. Non-opioid-based adjuvant analgesia in perioperative care. Contin Educ Anaesth Crit Care Pain. 2013;13(5):152-157. doi:10.1093/bjaceaccp/mkt012

66 Brown JT, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther. 2019;106(1):94-102. doi:10.1002/cpt.1409

67 Swen JJ, Nijenhuis M, Boer A de, et al. Pharmacogenetics: From Bench to Byte— An Update of Guidelines. Clin Pharmacol Ther. 2011;89(5):662-673. doi:10.1038/clpt.2011.34

68 Obeng AO, Hamadeh I, Smith M. Review of Opioid Pharmacogenetics and Considerations for Pain Management. Pharmacother J Hum Pharmacol Drug Ther. 2017;37(9):1105-1121. doi:10.1002/phar.1986

69 Moulton LS, Evans PA, Starks I, Smith T. Pre-operative education prior to elective hip arthroplasty surgery improves postoperative outcome. Int Orthop. 2015;39(8):1483-1486. doi:10.1007/s00264-015-2754-2

70 Ronco M, Iona L, Fabbro C, Bulfone G, Palese A. Patient education outcomes in surgery: a systematic review from 2004 to 2010. Int J Evid Based Healthc. 2012;10(4):309-323. doi:10.1111/j.1744-1609.2012.00286.x

71 American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 742: Postpartum Pain Management. Obstet Gynecol. 2018;132(1):e35-e43. doi:10.1097/AOG.0000000000002683

72 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. Chronic Pelvic Pain: ACOG Practice Bulletin, Number 218. Obstet Gynecol. 2020;135(3):e98-e109. doi:10.1097/AOG.0000000000003716

73 American College of Obstetricians and Gynecologists. ACOG Committee Opinion Number 760: Dysmenorrhea and Endometriosis in the Adolescent. ACOG. Published December 2018. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/12/dysmenorrhea-and-endometriosis-in-the-adolescent

74 What Americans believe about opioid prescription painkiller use. Presented at the: National Safety Council – Opioid Painkiller Media Briefing; 2015. Accessed December 16, 2019. https://www.nsc.org/Portals/0/Documents/NewsDocuments/031115-Public-Opinion-Poll.pdf

75 Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. Addiction. 2010;105(10):1776-1782. doi:10.1111/j.1360-0443.2010.03052.x

76 Miech R, Johnston L, O'Malley PM, Keyes KM, Heard K. Prescription Opioids in Adolescence and Future Opioid Misuse. Pediatrics. 2015;136(5):e1169-e1177. doi:10.1542/peds.2015-1364

77 Baehren DF, Marco CA, Droz DE, Sinha S, Callan EM, Akpunonu P. A Statewide Prescription Monitoring Program Affects Emergency Department Prescribing Behaviors. Ann Emerg Med. 2010;56(1):19-23.e3. doi:10.1016/j.annemergmed.2009.12.011

78 Prescription Drug Monitoring Program (PDMP) HOME | Division of Professions and Occupations. Colorado Department of Public Health & Environment (CDPHE). Accessed July 27, 2020. https://dpo.colorado.gov/PDMP

79 Cantrill SV, Brown MD, Carlisle RJ, et al. Clinical policy: critical issues in the prescribing of opioids for adult patients in the emergency department. Ann Emerg Med. 2012;60(4):499-525. doi:10.1016/j.annemergmed.2012.06.013

80 Colorado State Senate. Clinical Practice Measures for Safer Opioid Prescribing.; 2018.

81 Oderda GM, Said Q, Evans RS, et al. Opioid-Related Adverse Drug Events in Surgical Hospitalizations: Impact on Costs and Length of Stay. Ann Pharmacother. 2007;41(3):400-407. doi:10.1345/aph.1H386

82 Weingarten TN, Herasevich V, McGlinch MC, et al. Predictors of Delayed Postoperative Respiratory Depression Assessed From Naloxone Administration. Anesth Analg. 2015;121(2):422-429. doi:10.1213/ANE.0000000000000792

83 Lee JS, Hu HM, Brummett CM, et al. Postoperative Opioid Prescribing and the Pain Scores on Hospital Consumer Assessment of Healthcare Providers and Systems Survey. JAMA. 2017;317(19):2013-2015. doi:10.1001/jama.2017.2827

84 Substance Abuse and Mental Health Services Administration. Reports and Detailed Tables From the 2016 National Survey on Drug Use and Health (NSDUH). Published September 2016. Accessed September 15, 2019. https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2016-NSDUH.

85 Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage. 2004;28(2):140-175. doi:10.1016/j.jpainsymman.2004.05.002

References continued

86 Miller M, Barber CW, Leatherman S, et al. Prescription Opioid Duration of Action and the Risk of Unintentional Overdose Among Patients Receiving Opioid Therapy. JAMA Intern Med. 2015;175(4):608-615. doi:10.1001/jamainternmed.2014.8071

87 Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. Cochrane Database Syst Rev. 2011;(9). doi:10.1002/14651858.CD008659.pub2

88 Moore RA, Derry S, Aldington D, Wiffen PJ. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2015;(10):CD011407. doi:10.1002/14651858.CD011407.pub2

89 New York City Department of Health and Mental Hygeine. New York City Emergency Department Discharge Opioid Prescribing Guidelines. Published 2013. https://www1.nyc.gov/assets/doh/downloads/pdf/basas/opioid-prescribing-guidelines.pdf

90 Gong L, Stamer UM, Tzvetkov MV, Altman RB, Klein TE. PharmGKB summary: tramadol pathway. Pharmacogenet Genomics. 2014;24(7):374-380. doi:10.1097/FPC.0000000000000057

91 Thiels CA, Habermann EB, Hooten WM, Jeffery MM. Chronic use of tramadol after acute pain episode: cohort study. BMJ. 2019;365. doi:10.1136/bmj.l1849

92 Chung CP, Callahan ST, Cooper WO, et al. Individual short-acting opioids and the risk of opioid-related adverse events in adolescents. Pharmacoepidemiol Drug Saf. 2019;28(11):1448-1456. doi:10.1002/pds.4872

93 Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. Pain Med. 2016;17(1):85-98. doi:10.1111/pme.12907

94 Pawasauskas J, Stevens B, Youssef R, Kelley M. Predictors of naloxone use for respiratory depression and oversedation in hospitalized adults. Am J Health Syst Pharm. 2014;71(9):746-750. doi:10.2146/ajhp130568

95 Abrahamsson T, Berge J, Öjehagen A, Håkansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment—A nation-wide register-based open cohort study. Drug Alcohol Depend. 2017;174:58-64. doi:10.1016/j.drugalcdep.2017.01.013

96 American Medical Association. Promote safe storage and disposal of opioids and all medications. Published March 2017. https://www.aafp.org/dam/AAFP/documents/patient_care/pain_management/safe-storage.pdf

97 Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: mental health findings. Published November 2014. http://www.samhsa.gov/data/sites/default/files/NSDUHmhfr2013/NSDUHmhfr2013.pdf.

98 Substance Abuse and Mental Health Services Administration. Reports and Detailed Tables From the 2018 National Survey on Drug Use and Health (NSDUH). Published August 2019. https://www.samhsa.gov/data/report/2018-nsduh-detailed-tables.

99 Bailey JE, Campagna E, Dart RC, RADARS System Poison Center Investigators. The underrecognized toll of prescription opioid abuse on young children. Ann Emerg Med. 2009;53(4):419-424. doi:10.1016/j.annemergmed.2008.07.015

100 Finkelstein Y, Macdonald EM, Gonzalez A, et al. Overdose Risk in Young Children of Women Prescribed Opioids. Pediatrics. 2017;139(3). doi:10.1542/peds.2016-2887

101 Office on Women's Health. Final Report: Opioid Use, Misuse,and Overdose in Women. Published July 19, 2017. https://www.womenshealth.gov/files/documents/final-report-opioid-508.pdf

102 Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54). Published 2019. Accessed January 14, 2020. https://www.samhsa.gov/data/. August 2019

103 Gregorian R, Marrett E, Sivathanu V, et al. Safe Opioid Storage and Disposal: A Survey of Patient Beliefs and Practices. J Pain Res. 2020;13:987-995. doi:10.2147/JPR.S242825

104 U.S. Food and Drug Administration. Disposal of Unused Medicines: What You Should Know. Published February 1, 2019. Accessed September 12, 2019. http://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know.

105 Davies ED, Schneider F, Childs S, et al. A prevalence study of errors in opioid prescribing in a large teaching hospital. Int J Clin Pract. 2011;65(9):923-929. doi:10.1111/j.1742-1241.2011.02705.x

106 Office of the Surgeon General. Surgeon General's Advisory on Naloxone and Opioid Overdose. Published April 5, 2018. Accessed September 12, 2019. https://www.hhs.gov/surgeongeneral/priorities/opioids-and-addiction/naloxone-advisory/index.html.

107 Liang Y, Goros MW, Turner BJ. Drug Overdose: Differing Risk Models for Women and Men among Opioid Users with Non-Cancer Pain. Pain Med Malden Mass. 2016;17(12):2268-2279. doi:10.1093/pm/pnw071

108 Kaur M, Lee J. Treatment of Pediatric Opioid Overdose in the United States. Pediatrics. 2019;144(2 MeetingAbstract):00-00. doi:10.1542/peds.144.2_MeetingAbstract.00-n

109 Howard-Azzeh M, Pearl DL, O'Sullivan TL, Berke O. The identification of risk factors contributing to accidental opioid poisonings in companion dogs using data from a North American poison control center (2006-2014). PloS One. 2020;15(1):e0227701. doi:10.1371/journal.pone.0227701

110 Overdyk F, Dahan A, Roozekrans M, der Schrier R van, Aarts L, Niesters M. Opioid-induced respiratory depression in the acute care setting: a compendium of case reports. Pain Manag. 2014;4(4):317-325. doi:10.2217/pmt.14.19

111 Wang Y, Sands LP, Vaurio L, Mullen EA, Leung JM. The Effects of Postoperative Pain and Its Management on Postoperative Cognitive Dysfunction. Am J Geriatr Psychiatry. 2007;15(1):50-59. doi:10.1097/01.JGP.0000229792.31009.da

References continued

[112] Daoust R, Paquet J, Lavigne G, Piette É, Chauny J-M. Impact of Age, Sex and Route of Administration on Adverse Events after Opioid Treatment in the Emergency Department: A Retrospective Study. Pain Research and Management. doi:https://doi.org/10.1155/2015/316275

[113] Compton WM, Volkow ND. Abuse of prescription drugs and the risk of addiction. Drug Alcohol Depend. 2006;83:S4-S7. doi:10.1016/j.drugalcdep.2005.10.020

[114] Gordon DB. Acute pain assessment tools: let us move beyond simple pain ratings. Curr Opin Anesthesiol. 2015;28(5):565–569. doi:10.1097/ACO.0000000000000225

[115] Mularski RA, White-Chu F, Overbay D, Miller L, Asch SM, Ganzini L. Measuring Pain as the 5th Vital Sign Does Not Improve Quality of Pain Management. J Gen Intern Med. 2006;21(6):607-612. doi:10.1111/j.1525-1497.2006.00415.x

[116] Purser L, Warfield K, Richardson C. Making Pain Visible: An Audit and Review of Documentation to Improve the Use of Pain Assessment by Implementing Pain as the Fifth Vital Sign. Pain Manag Nurs. 2014;15(1):137-142. doi:10.1016/j.pmn.2012.07.007

[117] Zaslansky R, Rothaug J, Chapman CR, et al. PAIN OUT: The making of an international acute pain registry. Eur J Pain. 2015;19(4):490-502. doi:10.1002/ejp.571

[118] McCaffery M, Pasero C, Herr K. Pain Assessment and Pharmacologic Management. Mosby; 2011.

[119] Pasero C. One Size Does Not Fit All: Opioid Dose Range Orders. J Perianesth Nurs. 2014;29(3):246-252. doi:10.1016/j.jopan.2014.03.004

[120] Vila H, Smith RA, Augustyniak MJ, et al. The Efficacy and Safety of Pain Management Before and After Implementation of Hospital-Wide Pain Management Standards: Is Patient Safety Compromised by Treatment Based Solely on Numerical Pain Ratings?: Anesth Analg. 2005;101(2):474-480. doi:10.1213/01.ANE.0000155970.45321.A8

[121] van Dijk JFM, van Wijck AJM, Kappen TH, Peelen LM, Kalkman CJ, Schuurmans MJ. Postoperative pain assessment based on numeric ratings is not the same for patients and professionals: A cross-sectional study. Int J Nurs Stud. 2012;49(1):65-71. doi:10.1016/j.ijnurstu.2011.07.009

[122] Aubrun F, Salvi N, Coriat P, Riou B. Sex and Age related Differences in Morphine Requirements for Postoperative Pain Relief. Anesthesiol J Am Soc Anesthesiol. 2005;103(1):156-160.

[123] Halm M, Bailey C, St. Pierre J, et al. Pilot Evaluation of a Functional Pain Assessment Scale. Clin Nurse Spec. 2019;33(1):12–21. doi:10.1097/NUR.0000000000000416

[124] Gloth FM, Scheve AA, Stober CV, Chow S, Prosser J. The Functional Pain Scale: Reliability, Validity, and Responsiveness in an Elderly Population. J Am Med Dir Assoc. 2001;2(3):110-114. doi:10.1016/S1525-8610(04)70176-0

[125] National Academies of Sciences, Engineering and Medicine, Health and Medicine Division, Board on Health Sciences Policy, et al. Pain Management and the Intersection of Pain and Opioid Use Disorder. National Academies Press (US); 2017. Accessed March 7, 2020. http://www.ncbi.nlm.nih.gov/books/NBK458655/

[126] McGeary DD, McGeary CA, Gatchel RJ. A Comprehensive Review of Telehealth for Pain Management: Where We Are and The Way Ahead. Pain Pract. 2012;12(7):570-577. doi:10.1111/j.1533-2500.2012.00534.x

[127] Eaton LH, Gordon DB, Wyant S, et al. Development and implementation of a telehealth-enhanced intervention for pain and symptom management. Contemp Clin Trials. 2014;38(2):213-220. doi:10.1016/j.cct.2014.05.005

[128] Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: A systematic review. J Pain. 2002;3(3):159-180. doi:10.1054/jpai.2002.123652

[129] Sizar O, Gupta M. Opioid Induced Constipation. In: StatPearls. StatPearls Publishing; 2020. Accessed March 7, 2020. http://www.ncbi.nlm.nih.gov/books/NBK493184/

[130] Ebner F, Schulz SVW, de Gregorio A, et al. Prehabilitation in gynecological surgery? What do gynecologists know and need to know. Arch Gynecol Obstet. 2018;297(1):27-31. doi:10.1007/s00404-017-4565-8

[131] Miralpeix E, Mancebo G, Gayete S, Corcoy M, Solé-Sedeño J-M. Role and impact of multimodal prehabilitation for gynecologic oncology patients in an Enhanced Recovery After Surgery (ERAS) program. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2019;29(8):1235-1243. doi:10.1136/ijgc-2019-000597

[132] Chiang H-L, Chia Y-Y, Lin H-S, Chen C-H. The Implications of Tobacco Smoking on Acute Postoperative Pain: A Prospective Observational Study. Pain Research and Management. doi:https://doi.org/10.1155/2016/9432493

[133] Olson LC, Hong D, Conell-Price JS, Cheng S, Flood P. A transdermal nicotine patch is not effective for postoperative pain management in smokers: a pilot dose-ranging study. Anesth Analg. 2009;109(6):1987-1991. doi:10.1213/ANE.0b013e3181bd1612

[134] Nielsen PR, Andreasen J, Asmussen M, Tønnesen H. Costs and quality of life for prehabilitation and early rehabilitation after surgery of the lumbar spine. BMC Health Serv Res. 2008;8(1):209. doi:10.1186/1472-6963-8-209

[135] Banugo P, Amoako D. Prehabilitation. BJA Educ. 2017;17(12):401-405. doi:10.1093/bjaed/mkx032

[136] Ip HYV, Abrishami A, Peng PWH, Wong J, Chung F. Predictors of Postoperative Pain and Analgesic Consumption: A Qualitative Systematic Review. Anesthesiology. 2009;111(3):657-677. doi:10.1097/ALN.0b013e3181aae87a

[137] Møller AM, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet Lond Engl. 2002;359(9301):114-117. doi:10.1016/S0140-6736(02)07369-5

[138] Yang MMH, Hartley RL, Leung AA, et al. Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. BMJ Open. 2019;9(4):e025091. doi:10.1136/bmjopen-2018-025091

References continued

139 Theadom A, Cropley M. Effects of preoperative smoking cessation on the incidence and risk of intraoperative and postoperative complications in adult smokers: a systematic review. Tob Control. 2006;15(5):352-358. doi:10.1136/tc.2005.015263

140 InformedHealth.org. Can Quitting Smoking before Surgery Prevent Complications? Institute for Quality and Efficiency in Health Care (IQWiG); 2018. Accessed March 7, 2020. http://www.ncbi.nlm.nih.gov/books/NBK279556/

141 Thomsen T, Villebro N, Møller AM. Interventions for preoperative smoking cessation. Cochrane Database Syst Rev. 2014;(3):CD002294. doi:10.1002/14651858.CD002294.pub4

142 Tønnesen H, Schütten BT, Jørgensen BB. Influence of alcohol on morbidity after colonic surgery. Dis Colon Rectum. 1987;30(7):549-551. doi:10.1007/BF02554788

143 Tønneson H, Petersen KR, Nielsen HJ, et al. Postoperative morbidity among symptom-free alcohol misusers. The Lancet. 1992;340(8815):334-337. doi:10.1016/0140-6736(92)91405-W

144 Felding C, Jensen LM, Tønnesen H. Influence of alcohol intake on postoperative morbidityafter hysterectomy. Am J Obstet Gynecol. 1992;166(2):667-670. doi:10.1016/0002-9378(92)91695-7

145 Kao S-C, Tsai H-I, Cheng C-W, Lin T-W, Chen C-C, Lin C-S. The association between frequent alcohol drinking and opioid consumption after abdominal surgery: A retrospective analysis. PLoS ONE. 2017;12(3). doi:10.1371/journal.pone.0171275

146 Narita M, Miyoshi K, Narita M, Suzuki T. Functional reduction in μ-opioidergic system in the spinal cord under a neuropathic pain-like state following chronic ethanol consumption in the rat. Neuroscience. 2007;144(3):777-782. doi:10.1016/j.neuroscience.2006.10.028

147 Morisot N, Ron D. Alcohol-dependent molecular adaptations of the NMDA receptor system. Genes Brain Behav. 2017;16(1):139-148. doi:10.1111/gbb.12363

148 Tonnesen H, Rosenberg J, Nielsen HJ, et al. Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: randomised controlled trial. BMJ. 1999;318(7194):1311-1316. doi:10.1136/bmj.318.7194.1311

149 Oppedal K, Møller AM, Pedersen B, Tønnesen H. Preoperative alcohol cessation prior to elective surgery. Cochrane Database Syst Rev. 2012;(7):CD008343. doi:10.1002/14651858.CD008343.pub2

150 Elliott TE, Frail CK, Pawloski PA, Thomas AJ, Werner AM, Rossom RC. Opioid Use During Pregnancy, Observations of Opioid Use, and Secular Trend From 2006 to 2014 at HealthPartners Medical Group. Clin J Pain. 2018;34(8):707-712. doi:10.1097/AJP.0000000000000592

151 Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. Obstet Gynecol. 2014;123(5):997-1002. doi:10.1097/AOG.0000000000000208

152 Hilliard PE, Waljee J, Moser S, et al. Prevalence of Preoperative Opioid Use and Characteristics Associated With Opioid Use Among Patients Presenting for Surgery. JAMA Surg. 2018;153(10):929-937. doi:10.1001/jamasurg.2018.2102

153 Waljee J, Cron D, Steiger R, Zhong L, Englesbe M, Brummett C. The Effect of Preoperative Opioid Exposure on Healthcare Utilization and Expenditures Following Elective Abdominal Surgery. Ann Surg. 2017;265(4):715-721. doi:10.1097/SLA.0000000000002117

154 Cron DC, Englesbe MJ, Bolton CJ, et al. Preoperative Opioid Use is Independently Associated With Increased Costs and Worse Outcomes After Major Abdominal Surgery. Ann Surg. 2017;265(4):695-701. doi:10.1097/SLA.0000000000001901

155 Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14(2):145-161.

156 U.S. Department of Health and Human Services. HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics. Published online October 2019. Accessed December 2, 2019. https://www.cms.gov/About-CMS/Story-Page/CDCs-Tapering-Guidance.pdf

157 American Society of Regional Anesthesia and Pain Medicine. Safe opioid storage, tapering, and disposal. Accessed December 8, 2019. https://www.asra.com/page/2725/safe-opioid-storage-tapering-and-disposal

158 Mayo Clinic. Tapering off opioids: When and how. Accessed December 8, 2019. https://www.mayoclinic.org/diseases-conditions/prescription-drug-abuse/in-depth/tapering-off-opioids-when-and-how/art-20386036

159 Department of Veterans Affairs and the Department of Defense. Opioid Tapering Booklet. Published June 2017. Accessed December 8, 2019. https://www.qmo.amedd.army.mil/OT/OpioidTaperingBooklet_FINAL_508.pdf

160 Centers for Disease Control and Prevention. POCKET GUIDE: TAPERING OPIOIDS FOR CHRONIC PAIN. Accessed December 8, 2019. https://www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf

161 Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Intern Med. 2016;176(9):1286-1293. doi:10.1001/jamainternmed.2016.3298

162 Burcher KM, Suprun A, Smith A. Risk Factors for Opioid Use Disorders in Adult Postsurgical Patients. Cureus. 2018;10(5). doi:10.7759/cureus.2611

163 Cheatle MD, Compton PA, Dhingra L, Wasser TE, O'Brien CP. Development of the Revised Opioid Risk Tool to Predict Opioid Use Disorder in Patients with Chronic Nonmalignant Pain. J Pain. 2019;20(7):842-851. doi:10.1016/j.jpain.2019.01.011

164 Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the Revised Screener and Opioid Assessment for Patients With Pain (SOAPP-R). J Pain. 2008;9(4):360-372. doi:10.1016/j.jpain.2007.11.014

165 Webster LR, Webster RM. Predicting Aberrant Behaviors in Opioid-Treated Patients: Preliminary Validation of the Opioid Risk Tool. Pain Med. 2005;6(6):432-442. doi:10.1111/j.1526-4637.2005.00072.x

References continued

166 Klimas J, Gorfinkel L, Fairbairn N, et al. Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain: A Systematic Review. JAMA Netw Open. 2019;2(5):e193365-e193365. doi:10.1001/jamanetworkopen.2019.3365

167 Hooten WM, St Sauver JL, McGree ME, Jacobson DJ, Warner DO. Incidence and Risk Factors for Progression From Short-term to Episodic or Long-term Opioid Prescribing: A Population-Based Study. Mayo Clin Proc. 2015;90(7):850-856. doi:10.1016/j.mayocp.2015.04.012

168 Nicholson AD, Kassam HF, Steele JL, Passarelli NR, Blaine TA, Kovacevic D. Development of a clinical risk calculator for prolonged opioid use after shoulder surgery. J Shoulder Elbow Surg. 2019;28(11):2225-2231. doi:10.1016/j.jse.2019.03.033

169 Edlund MJ, Martin BC, Fan M-Y, Devries A, Braden JB, Sullivan MD. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: Results from the TROUP Study. Drug Alcohol Depend. 2010;112(1):90-98. doi:10.1016/j.drugalcdep.2010.05.017

170 Cochran BN, Flentje A, Heck NC, et al. Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: Mathematical modeling using a database of commercially-insured individuals. Drug Alcohol Depend. 2014;138:202-208. doi:10.1016/j.drugalcdep.2014.02.701

171 Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ. 2014;348. doi:10.1136/bmj.g1251

172 Jungquist CR, Quinlan-Colwell A, Vallerand A, et al. American Society for Pain Management Nursing Guidelines on Monitoring for Opioid-Induced Advancing Sedation and Respiratory Depression: Revisions. Pain Manag Nurs Off J Am Soc Pain Manag Nurses. 2020;21(1):7-25. doi:10.1016/j.pmn.2019.06.007

173 Nadpara PA, Joyce AR, Murrelle EL, et al. Risk Factors for Serious Prescription Opioid-Induced Respiratory Depression or Overdose: Comparison of Commercially Insured and Veterans Health Affairs Populations. Pain Med. 2018;19(1):79-96. doi:10.1093/pm/pnx038

174 Danovitch I, Vanle B, Van Groningen N, Ishak W, Nuckols T. Opioid Overdose in the Hospital Setting: A Systematic Review. J Addict Med. 2020;14(1):39–47. doi:10.1097/ADM.0000000000000536

175 Kalkman CJ, Visser K, Moen J, Bonsel GJ, Grobbee DE, Moons KGM. Preoperative prediction of severe postoperative pain. Pain. 2003;105(3):415-423. doi:10.1016/S0304-3959(03)00252-5

176 Moerman N, van Dam FSAM, Muller MJ, Oosting H. The Amsterdam Preoperative Anxiety and Information Scale (APAIS). Anesth Analg. 1996;82(3):445–451.

177 Laufenberg-Feldmann R, Kappis B. Assessing preoperative anxiety using a questionnaire and clinical rating: A prospective observational study. Eur J Anaesthesiol. 2013;30(12):758-763. doi:10.1097/EJA.0b013e3283631751

178 Mathews A, Ridgeway V. Personality and surgical recovery: A review. Br J Clin Psychol. 1981;20(4):243-260. doi:10.1111/j.2044-8260.1981.tb00525.x

179 Domar AD, Everett LL, Keller MG. Preoperative anxiety: is it a predictable entity? Anesth Analg. 1989;69(6):763-767.

180 Kjølhede P, Wodlin NB, Nilsson L, Fredrikson M, Wijma K. Impact of stress coping capacity on recovery from abdominal hysterectomy in a fast-track programme: a prospective longitudinal study. BJOG Int J Obstet Gynaecol. 2012;119(8):998-1007. doi:10.1111/j.1471-0528.2012.03342.x

181 Zhao S, Chen F, Feng A, Han W, Zhang Y. Risk Factors and Prevention Strategies for Postoperative Opioid Abuse. Pain Research and Management. doi:https://doi.org/10.1155/2019/7490801

182 VanDenKerkhof EG, Hopman WM, Goldstein DH, et al. Impact of Perioperative Pain Intensity, Pain Qualities, and Opioid Use on Chronic Pain After Surgery: A Prospective Cohort Study. Reg Anesth Pain Med. 2012;37(1):19-27. doi:10.1097/AAP.0b013e318237516e

183 Brandsborg B, Nikolajsen L. Chronic pain after hysterectomy. Curr Opin Anaesthesiol. 2018;31(3):268-273. doi:10.1097/ACO.0000000000000586

184 Pinto PR, McIntyre T, Nogueira-Silva C, Almeida A, Araújo-Soares V. Risk factors for persistent postsurgical pain in women undergoing hysterectomy due to benign causes: a prospective predictive study. J Pain Off J Am Pain Soc. 2012;13(11):1045-1057. doi:10.1016/j.jpain.2012.07.014

185 American Society of Regional Anesthesia and Pain Medicine. Truncal Blocks for Cesarean Pain: Filling a Void in Obstetric Pain Management. Published May 2018. https://www.asra.com/asra-news/article/56/truncal-blocks-for-cesarean-pain-filling

186 Reddi D. Preventing chronic postoperative pain. Anaesthesia. 2016;71 Suppl 1:64-71. doi:10.1111/anae.13306

187 Althaus A, Hinrichs-Rocker A, Chapman R, et al. Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain. 2012;16(6):901-910. doi:10.1002/j.1532-2149.2011.00090.x

188 Thapa P, Euasobhon P. Chronic postsurgical pain: current evidence for prevention and management. Korean J Pain. 2018;31(3):155-173. doi:10.3344/kjp.2018.31.3.155

189 Munro A, Sjaus A, George RB. Anesthesia and analgesia for gynecological surgery. Curr Opin Anaesthesiol. 2018;31(3):274-279. doi:10.1097/ACO.0000000000000584

190 Weinstein EJ, Levene JL, Cohen MS, et al. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. Cochrane Database Syst Rev. 2018;(6). doi:10.1002/14651858.CD007105.pub4

191 Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. BJA Br J Anaesth. 2013;111(5):711-720. doi:10.1093/bja/aet213

References continued

192 Calcaterra SL, Yamashita TE, Min S-J, Keniston A, Frank JW, Binswanger IA. Opioid Prescribing at Hospital Discharge Contributes to Chronic Opioid Use. J Gen Intern Med. 2016;31(5):478-485. doi:10.1007/s11606-015-3539-4

193 Deyo RA, Hallvik SE, Hildebran C, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study. J Gen Intern Med. 2017;32(1):21-27. doi:10.1007/s11606-016-3810-3

194 Franklin GM, Stover BD, Turner JA, Fulton-Kehoe D, Wickizer TM. Early Opioid Prescription and Subsequent Disability Among Workers With Back Injuries: The Disability Risk Identification Study Cohort. Spine. 2008;33(2):199–204. doi:10.1097/BRS.0b013e318160455c

195 Webster BS, Verma SK, Gatchel RJ. Relationship Between Early Opioid Prescribing for Acute Occupational Low Back Pain and Disability Duration, Medical Costs, Subsequent Surgery and Late Opioid Use. Spine. 2007;32(19):2127–2132. doi:10.1097/BRS.0b013e318145a731

196 Prabhu M, Dubois H, James K, et al. Implementation of a Quality Improvement Initiative to Decrease Opioid Prescribing After Cesarean Delivery. Obstet Gynecol. 2018;132(3):631-636. doi:10.1097/AOG.0000000000002789

197 Osmundson SS, Raymond BL, Kook BT, et al. Individualized Compared With Standard Postdischarge Oxycodone Prescribing After Cesarean Birth: A Randomized Controlled Trial. Obstet Gynecol. 2018;132(3):624-630. doi:10.1097/AOG.0000000000002782

198 Overton HN, Hanna MN, Bruhn WE, et al. Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus. J Am Coll Surg. 2018;227(4):411-418. doi:10.1016/j.jamcollsurg.2018.07.659

199 Hill MV, Stucke RS, Billmeier SE, Kelly JL, Barth RJ. Guideline for Discharge Opioid Prescriptions after Inpatient General Surgical Procedures. J Am Coll Surg. 2018;226(6):996-1003. doi:10.1016/j.jamcollsurg.2017.10.012

200 Michigan Opioid Prescribing Engagement Network (Michigan OPEN). Prescribing Recommendations. Published July 1, 2019. https://michigan-open.org/prescribing-recommendations/

201 Nataraj N, Zhang K, Guy GP, Losby JL. Identifying opioid prescribing patterns for high-volume prescribers via cluster analysis. Drug Alcohol Depend. 2019;197:250-254. doi:10.1016/j.drugalcdep.2019.01.012

202 Levy B, Paulozzi L, Mack KA, Jones CM. Trends in Opioid Analgesic–Prescribing Rates by Specialty, U.S., 2007–2012. Am J Prev Med. 2015;49(3):409-413. doi:10.1016/j.amepre.2015.02.020

203 Guy GP, Zhang K. Opioid Prescribing by Specialty and Volume in the U.S. Am J Prev Med. 2018;55(5):e153-e155. doi:10.1016/j.amepre.2018.06.008

204 The MITRE Corporation. Enhancing Access to Prescription Drug Monitoring Programs Using Health Information Technology: Integrating Health IT and PDMPs to Improve Patient Care. Published 2013. Accessed September 12, 2019. https://www.healthit.gov/sites/default/files/connecting_for_impact-final-508.pdf

205 The MITRE Corporation. Enhancing Access to Prescription Drug Monitoring Programs Using Health Information Technology: Connecting Prescribers and Dispensers to PDMPs through Health IT: Six Pilot Studies and Their Impact. Published 2012. Accessed September 12, 2019. https://www.healthit.gov/sites/default/files/pdmp_pilot_studies_summary_0.pdf.

206 Anson P. AMA Drops Pain as Vital Sign. Pain News Network. Published June 16, 2016. https://www.painnewsnetwork.org/stories/2016/6/16/ama-drops-pain-as-vital-sign

207 The United States Department of Health & Human Services. Pain Management Best Practices. Published May 9, 2019. Accessed February 12, 2020. https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf

208 Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain Off J Am Pain Soc. 2009;10(5):447-485. doi:10.1016/j.jpain.2008.12.001

209 Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain Off J Am Pain Soc. 2008;9(10):883-891. doi:10.1016/j.jpain.2008.05.005

210 Unruh AM. Gender variations in clinical pain experience. Pain. 1996;65(2-3):123-167. doi:10.1016/0304-3959(95)00214-6

211 Sorge RE, LaCroix-Fralish ML, Tuttle AH, et al. Spinal cord Toll-like receptor 4 mediates inflammatory and neuropathic hypersensitivity in male but not female mice. J Neurosci Off J Soc Neurosci. 2011;31(43):15450-15454. doi:10.1523/JNEUROSCI.3859-11.2011

212 Shipton EE, Bate F, Garrick R, Steketee C, Shipton EA, Visser EJ. Systematic Review of Pain Medicine Content, Teaching, and Assessment in Medical School Curricula Internationally. Pain Ther. 2018;7(2):139-161. doi:10.1007/s40122-018-0103-z

213 Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. Anesth Analg. 2003;97(2):534–540. doi:10.1213/01.ANE.0000068822.10113.9E

214 Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin. 2014;30(1):149-160. doi:10.1185/03007995.2013.860019

215 Kessler ER, Shah M, Gruschkus SK, Raju A. Cost and Quality Implications of Opioid-Based Postsurgical Pain Control Using Administrative Claims Data from a Large Health System: Opioid-Related Adverse Events and Their Impact on Clinical and Economic Outcomes. Pharmacother J Hum Pharmacol Drug Ther. 2013;33(4):383-391. doi:10.1002/phar.1223

216 Shafi S, Collinsworth AW, Copeland LA, et al. Association of Opioid-Related Adverse Drug Events With Clinical and Cost Outcomes Among Surgical Patients in a Large Integrated Health Care Delivery System. JAMA Surg. 2018;153(8):757-763. doi:10.1001/jamasurg.2018.1039

References continued

217 Minkowitz HS, Scranton R, Gruschkus SK, Nipper-Johnson K, Menditto L, Dandappanavar A. Development and Validation of a Risk Score to Identify Patients at High Risk for Opioid-Related Adverse Drug Events. J Manag Care Pharm. 2014;20(9):948-958. doi:10.18553/jmcp.2014.20.9.948

218 Mathew B, Lennon FE, Siegler JH, et al. Novel Role of the Mu Opioid Receptor in Lung Cancer Progression: A Laboratory Study. Anesth Analg. 2011;112(3):558-567. doi:10.1213/ANE.0b013e31820568af

219 Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. The Lancet. 2006;367(9522):1618-1625. doi:10.1016/S0140-6736(06)68700-X

220 Searle RD, Simpson MP, Simpson KH, Milton R, Bennett MI. Can chronic neuropathic pain following thoracic surgery be predicted during the postoperative period? Interact Cardiovasc Thorac Surg. 2009;9(6):999-1002. doi:10.1510/icvts.2009.216887

221 Gerbershagen HJ. Transition from acute to chronic postsurgical pain. Physiology, risk factors and prevention. Schmerz Berl Ger. 2013;27(1):81-93; quiz 94-95. doi:10.1007/s00482-012-1287-5

222 Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. PAIN Rep. 2017;2(6):e627. doi:10.1097/PR9.0000000000000627

223 Ladha KS, Patorno E, Huybrechts KF, Liu J, Rathmell JP, Bateman BT. Variations in the Use of Perioperative Multimodal Analgesic Therapy. Anesthesiol J Am Soc Anesthesiol. 2016;124(4):837-845. doi:10.1097/ALN.0000000000001034

224 Curatolo M, Sveticic G. Drug combinations in pain treatment: a review of the published evidence and a method for finding the optimal combination. Best Pract Res Clin Anaesthesiol. 2002;16(4):507-519. doi:10.1053/bean.2002.0254

225 American Society of Anesthesiologists Task Force on Acute Pain. Practice guidelines for acute pain management in the perioperative setting : an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012;116:248-273.

226 Kumar K, Kirksey MA, Duong S, Wu CL. A Review of Opioid-Sparing Modalities in Perioperative Pain Management: Methods to Decrease Opioid Use Postoperatively. Anesth Analg. 2017;125(5):1749-1760. doi:10.1213/ANE.0000000000002497

227 Joshi GP, Kehlet H, Beloeil H, et al. Guidelines for perioperative pain management: need for re-evaluation. Br J Anaesth. 2017;119(4):720-722. doi:10.1093/bja/aex304

228 Committee Opinion No. 750: Perioperative Pathways: Enhanced Recovery After Surgery: Correction. Obstet Gynecol. 2019;133(6):1288. doi:10.1097/AOG.0000000000003312

229 Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. JAMA Surg. 2017;152(3):292-298. doi:10.1001/jamasurg.2016.4952

230 Pędziwiatr M, Wierdak M, Nowakowski M, et al. Cost minimization analysis of laparoscopic surgery for colorectal cancer within the enhanced recovery after surgery (ERAS) protocol: a single-centre, case-matched study. Videosurgery Miniinvasive Tech. 2016;11(1):14-21. doi:10.5114/wiitm.2016.58617

231 Ljungqvist O. ERAS--enhanced recovery after surgery: moving evidence-based perioperative care to practice. JPEN J Parenter Enteral Nutr. 2014;38(5):559-566. doi:10.1177/0148607114523451

232 Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review. JAMA Surg. 2017;152(7):691-697. doi:10.1001/jamasurg.2017.0898

233 Kehlet H, Wilmore DW. Evidence-Based Surgical Care and the Evolution of Fast-Track Surgery. Ann Surg. 2008;248(2):189–198. doi:10.1097/SLA.0b013e31817f2c1a

234 Scott MJ, Baldini G, Fearon KCH, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations. Acta Anaesthesiol Scand. 2015;59(10):1212-1231. doi:10.1111/aas.12601

235 Joshi GP, Kehlet H. Enhanced Recovery Pathways: Looking Into the Future. Anesth Analg. 2019;128(1):5–7. doi:10.1213/ANE.0000000000003746

236 Moningi S, Patki A, Padhy N, Ramachandran G. Enhanced recovery after surgery: An anesthesiologist's perspective. J Anaesthesiol Clin Pharmacol. 2019;35(Suppl 1):S5-S13. doi:10.4103/joacp.JOACP_238_16

237 Phelps P, Cakmakkaya OS, Apfel CC, Radke OC. A simple clinical maneuver to reduce laparoscopy-induced shoulder pain: a randomized controlled trial. Obstet Gynecol. 2008;111(5):1155-1160. doi:10.1097/AOG.0b013e31816e34b4

238 Nguyen NT, Furdui G, Fleming NW, et al. Effect of heated and humidified carbon dioxide gas on core temperature and postoperative pain: a randomized trial. Surg Endosc. 2002;16(7):1050-1054. doi:10.1007/s00464-001-8237-0

239 Sammour T, Kahokehr A, Hill AG. Meta-analysis of the effect of warm humidified insufflation on pain after laparoscopy. Br J Surg. 2008;95(8):950-956. doi:10.1002/bjs.6304

240 Fredman B, Shapiro A, Zohar E, et al. The analgesic efficacy of patient-controlled ropivacaine instillation after Cesarean delivery. Anesth Analg. 2000;91(6):1436-1440. doi:10.1097/00000539-200012000-00025

241 O'Neill P, Duarte F, Ribeiro I, Centeno MJ, Moreira J. Ropivacaine continuous wound infusion versus epidural morphine for postoperative analgesia after cesarean delivery: a randomized controlled trial. Anesth Analg. 2012;114(1):179-185. doi:10.1213/ANE.0b013e3182368e87

242 Lalmand M, Wilwerth M, Fils J-F, Van der Linden P. Continuous Ropivacaine Subfascial Wound Infusion Compared With Intrathecal Morphine for Postcesarean Analgesia: A Prospective, Randomized Controlled, Double-Blind Study. Anesth Analg. 2017;125(3):907-912. doi:10.1213/ANE.0000000000001892

243 Bucklin BA. Postpartum tubal ligation: timing and other anesthetic considerations. Clin Obstet Gynecol. 2003;46(3):657-666. doi:10.1097/00003081-200309000-00018

References continued

244 Marks JL, Ata B, Tulandi T. Systematic review and metaanalysis of intraperitoneal instillation of local anesthetics for reduction of pain after gynecologic laparoscopy. J Minim Invasive Gynecol. 2012;19(5):545-553. doi:10.1016/j.jmig.2012.04.002

245 Arden D, Seifert E, Donnellan N, Guido R, Lee T, Mansuria S. Intraperitoneal instillation of bupivacaine for reduction of postoperative pain after laparoscopic hysterectomy: a double-blind randomized controlled trial. J Minim Invasive Gynecol. 2013;20(5):620-626. doi:10.1016/j.jmig.2013.03.012

246 Shahin AY, Osman AM. Intraperitoneal lidocaine instillation and postcesarean pain after parietal peritoneal closure: a randomized double blind placebo-controlled trial. Clin J Pain. 2010;26(2):121-127. doi:10.1097/AJP.0b013e3181b99ddd

247 Gurusamy KS, Nagendran M, Guerrini GP, Toon CD, Zinnuroglu M, Davidson BR. Intraperitoneal local anaesthetic instillation versus no intraperitoneal local anaesthetic instillation for laparoscopic cholecystectomy. Cochrane Database Syst Rev. 2014;(3). doi:10.1002/14651858.CD007337.pub3

248 Bamigboye AA, Justus HG. Ropivacaine abdominal wound infiltration and peritoneal spraying at cesarean delivery for preemptive analgesia. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2008;102(2):160-164. doi:10.1016/j.ijgo.2008.03.019

249 Visalyaputra S, Lertakyamanee J, Pethpaisit N, Somprakit P, Parakkamodom S, Suwanapeum P. Intraperitoneal lidocaine decreases intraoperative pain during postpartum tubal ligation. Anesth Analg. 1999;88(5):1077-1080. doi:10.1097/00000539-199905000-00020

250 Patel R, Carvalho JCA, Downey K, Kanczuk M, Bernstein P, Siddiqui N. Intraperitoneal Instillation of Lidocaine Improves Postoperative Analgesia at Cesarean Delivery: A Randomized, Double-Blind, Placebo-Controlled Trial. Anesth Analg. 2017;124(2):554-559. doi:10.1213/ANE.0000000000001799

251 Werntz M, Burwick R, Togioka B. Intraperitoneal chloroprocaine is a useful adjunct to neuraxial block during cesarean delivery: a case series. Int J Obstet Anesth. 2018;35:33-41. doi:10.1016/j.ijoa.2018.01.007

252 Jha N, Jha AK. Intraperitoneal Instillation of Local Anesthetics: Is This a Suitable Alternative for Postcesarean Pain Relief Without Toxicity Profiling? Anesth Analg. 2017;125(1):352. doi:10.1213/ANE.0000000000002136

253 Lavand'homme P. Opioid-free anaesthesia: Pro: damned if you don't use opioids during surgery. Eur J Anaesthesiol EJA. 2019;36(4):247–249. doi:10.1097/EJA.0000000000000966

254 Mulier JP. Is opioid-free general anesthesia for breast and gynecological surgery a viable option? Curr Opin Anaesthesiol. 2019;32(3):257-262. doi:10.1097/ACO.0000000000000716

255 Hakim KYK, Wahba WZB. Opioid-Free Total Intravenous Anesthesia Improves Postoperative Quality of Recovery after Ambulatory Gynecologic Laparoscopy. Anesth Essays Res. 2019;13(2):199-203. doi:10.4103/aer.AER_74_19

256 Kamdar NV, Hoftman N, Rahman S, Cannesson M. Opioid-Free Analgesia in the Era of Enhanced Recovery After Surgery and the Surgical Home: Implications for Postoperative Outcomes and Population Health. Anesth Analg. 2017;125(4):1089–1091. doi:10.1213/ANE.0000000000002122

257 Joly V, Richebe P, Guignard B, et al. Remifentanil-induced Postoperative Hyperalgesia and Its Prevention with Small-dose Ketamine. Anesthesiol J Am Soc Anesthesiol. 2005;103(1):147-155.

258 Angst MS. Intraoperative Use of Remifentanil for TIVA: Postoperative Pain, Acute Tolerance, and Opioid-Induced Hyperalgesia. J Cardiothorac Vasc Anesth. 2015;29:S16-S22. doi:10.1053/j.jvca.2015.01.026

259 Rivat C, Ballantyne J. The dark side of opioids in pain management: basic science explains clinical observation. Pain Rep. 2016;1(2). doi:10.1097/PR9.0000000000000570

260 Nassif GJ, Miller TE. Evolving the management of acute perioperative pain towards opioid free protocols: a narrative review. Curr Med Res Opin. 2019;35(12):2129-2136. doi:10.1080/03007995.2019.1646001

261 Smith AM, Young P, Blosser CC, Poole AT. Multimodal Stepwise Approach to Reducing In-Hospital Opioid Use After Cesarean Delivery: A Quality Improvement Initiative. Obstet Gynecol. 2019;133(4):700-706. doi:10.1097/AOG.0000000000003156

262 Valentine AR, Carvalho B, Lazo TA, Riley ET. Scheduled acetaminophen with as-needed opioids compared to as-needed acetaminophen plus opioids for post-cesarean pain management. Int J Obstet Anesth. 2015;24(3):210-216. doi:10.1016/j.ijoa.2015.03.006

263 Arıkan M, Aslan B, Arıkan O, Horasanlı E, But A. Comparison of the effects of magnesium and ketamine on postoperative pain and morphine consumption. A double-blind randomized controlled clinical study. Acta Cir Bras. 2016;31(1):67-73. doi:10.1590/S0102-865020160010000010

264 Tang C, Xia Z. Dexmedetomidine in perioperative acute pain management: a non-opioid adjuvant analgesic. J Pain Res. 2017;10:1899-1904. doi:10.2147/JPR.S139387

265 Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of Perioperative Systemic α2 Agonists on Postoperative Morphine Consumption and Pain IntensitySystematic Review and Meta-analysis of Randomized Controlled Trials. Anesthesiol J Am Soc Anesthesiol. 2012;116(6):1312-1322. doi:10.1097/ALN.0b013e31825681cb

266 Zhong W-G, Ge X-Y, Zhu H, et al. Dexmedetomidine for antiemesis in gynecologic surgery: a meta-analysis of randomized controlled trials. Int J Clin Exp Med. 2015;8(9):14566-14576.

267 Menshawi MA, Fahim HM. Dexmedetomidine versus lidocaine as an adjuvant to general anesthesia for elective abdominal gynecological surgeries. Ain-Shams J Anesthesiol. 2019;11(1):12. doi:10.1186/s42077-019-0027-9

268 Xu S-Q, Li Y-H, Wang S-B, Hu S-H, Ju X, Xiao J-B. Effects of intravenous lidocaine, dexmedetomidine and their combination on postoperative pain and bowel function recovery after abdominal hysterectomy. Minerva Anestesiol. 2017;83(7):685-694. doi:10.23736/S0375-9393.16.11472-5

References continued

269 Ao L, Shi J, Bai Y, Zheng Y, Gan J. Effectiveness and safety of intravenous application of dexmedetomidine for cesarean section under general anesthesia: a meta-analysis of randomized trials. Drug Des Devel Ther. 2019;13:965-974. doi:10.2147/DDDT.S197165

270 Kong D, Bai J, Ma S, Li C, Yang L, Kong X. Effects of dexmedetomidine hydrochloride on hemodynamics, postoperative analgesia and cognition in cesarean section. Exp Ther Med. 2018;16(3):1778-1783. doi:10.3892/etm.2018.6363

271 Yu Z, Zhang P, Wang H, et al. Effects of dexmedetomidine versus remifentanil on mothers and neonates during cesarean section under general anesthesia. Biomed Pap Med Fac Univ Palacky Olomouc Czechoslov. Published online November 19, 2019. doi:10.5507/bp.2019.055

272 Carabine UA, Milligan KR, Moore JA. Adrenergic modulation of preoperative anxiety: a comparison of temazepam, clonidine, and timolol. Anesth Analg. 1991;73(5):633-637. doi:10.1213/00000539-199111000-00021

273 Rhee KY. Intravenous Clonidine Prolongs Spinal Anesthesia after Hyperbaric Bupivacaine. Korean J Anesthesiol. 2003;44(3):354-358. doi:2003.44.3.354

274 Whizar-Lugo V, Flores-Carrillo J, Preciado-Ramirez S. Intrathecal Clonidine as Spinal Anaesthesia Adjuvant — Is there a Magical Dose? In: Topics in Spinal Anaesthesia. IntechOpen; 2014. https://www.intechopen.com/books/topics-in-spinal-anaesthesia/intrathecal-clonidine-as-spinal-anaesthesia-adjuvant-is-there-a-magical-dose-

275 Behdad S, Ayatollahi V, Yazdi AG, Mortazavizadeh A, Niknam F. Effect of oral low dose clonidine premedication on postoperative pain in patients undergoing abdominal hysterectomy: a randomized placebo controlled clinical trial. Rev Med Chir Soc Med Nat Iasi. 2013;117(4):934-941.

276 Heesen M, Böhmer J, Brinck ECV, et al. Intravenous ketamine during spinal and general anaesthesia for caesarean section: systematic review and meta-analysis. Acta Anaesthesiol Scand. 2015;59(4):414-426. doi:10.1111/aas.12468

277 McKeown A, Seppi V, Hodgson R. Intravenous Magnesium Sulphate for Analgesia after Caesarean Section: A Systematic Review. Anesthesiology Research and Practice. doi:https://doi.org/10.1155/2017/9186374

278 National Center for Biotechnology Information. Analgesic Efficacy of Continuous Intravenous Magnesium Infusion as an Adjuvant to Morphine for Postoperative Analgesia: A Systematic Review and Meta-Analysis. Centre for Reviews and Dissemination (UK); 2013. Accessed March 2, 2020. http://www.ncbi.nlm.nih.gov/books/NBK159491/

279 Haryalchi K, Abedinzade M, Khanaki K, Mansour Ghanaie M, Mohammad Zadeh F. Whether preventive low dose magnesium sulphate infusion has an influence on postoperative pain perception and the level of serum beta-endorphin throughout the total abdominal hysterectomy. Rev Esp Anestesiol Reanim. 2017;64(7):384-390. doi:10.1016/j.redar.2016.11.009

280 Taheri A, Haryalchi K, Mansour Ghanaie M, Habibi Arejan N. Effect of low-dose (single-dose) magnesium sulfate on postoperative analgesia in hysterectomy patients receiving balanced general anesthesia. Anesthesiol Res Pract. 2015;2015:306145. doi:10.1155/2015/306145

281 Wang S-C, Pan P-T, Chiu H-Y, Huang C-J. Neuraxial magnesium sulfate improves postoperative analgesia in Cesarean section delivery women: A meta-analysis of randomized controlled trials. Asian J Anesthesiol. 2017;55(3):56-67. doi:10.1016/j.aja.2017.06.005

282 Apan A, Buyukkocak U, Ozcan S, Sarı F, Basar H. Postoperative magnesium sulphate infusion reduces analgesic requirements in spinal anaesthesia. Eur J Anaesthesiol. 2004;21(10):766-769. doi:10.1017/S026502150400002X

283 Ryu J-H, Kang M-H, Park K-S, Do S-H. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. BJA Br J Anaesth. 2008;100(3):397-403. doi:10.1093/bja/aem407

284 Seyhan TO, Tugrul M, Sungur MO, et al. Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery. BJA Br J Anaesth. 2006;96(2):247-252. doi:10.1093/bja/aei291

285 Gupta K, Vohra V, Sood J. The role of magnesium as an adjuvant during general anaesthesia. Anaesthesia. 2006;61(11):1058-1063. doi:10.1111/j.1365-2044.2006.04801.x

286 King MR, Ladha KS, Gelineau AM, Anderson TA. Perioperative Dextromethorphan as an Adjunct for Postoperative Pain: A Meta-analysis of Randomized Controlled Trials. Anesthesiology. 2016;124(3):696-705. doi:10.1097/ALN.0000000000000950

287 Ilkjaer S, Bach LF, Nielsen PA, Wernberg M, Dahl JB. Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy. Pain. 2000;86(1-2):19-24. doi:10.1016/s0304-3959(99)00305-x

288 Lu C-H, Liu J-Y, Lee M-S, et al. Preoperative cotreatment with dextromethorphan and ketorolac provides an enhancement of pain relief after laparoscopic-assisted vaginal hysterectomy. Clin J Pain. 2006;22(9):799-804. doi:10.1097/01.ajp.0000210931.20322.da

289 Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2015;(9):CD008659. doi:10.1002/14651858.CD008659.pub3

290 Moore PA, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions: translating clinical research to dental practice. J Am Dent Assoc 1939. 2013;144(8):898-908. doi:10.14219/jada.archive.2013.0207

291 Bandolier. Oxford League Table of Analgesic Efficacy. Accessed July 28, 2020. http://www.bandolier.org.uk/booth/painpag/Acutrev/Analgesics/lftab.html

292 Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DGA, Manning MW. The rising tide of opioid use and abuse: the role of the anesthesiologist. Perioper Med. 2018;7(1):16. doi:10.1186/s13741-018-0097-4

References continued

293 Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. Anesthesiology. 2005;102(4):822-831. doi:10.1097/00000542-200504000-00019

294 Saurabh S, Smith JK, Pedersen M, Jose P, Nau P, Samuel I. Scheduled intravenous acetaminophen reduces postoperative narcotic analgesic demand and requirement after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis Off J Am Soc Bariatr Surg. 2015;11(2):424-430. doi:10.1016/j.soard.2014.09.017

295 Savarese JJ, Tabler NG. Multimodal analgesia as an alternative to the risks of opioid monotherapy in surgical pain management. J Healthc Risk Manag. 2017;37(1):24-30. doi:10.1002/jhrm.21262

296 Garland EL, Baker AK, Larsen P, et al. Randomized Controlled Trial of Brief Mindfulness Training and Hypnotic Suggestion for Acute Pain Relief in the Hospital Setting. J Gen Intern Med. 2017;32(10):1106-1113. doi:10.1007/s11606-017-4116-9

297 Arumugam S, Lau CS, Chamberlain RS. Use of preoperative gabapentin significantly reduces postoperative opioid consumption: a meta-analysis. Journal of Pain Research. doi:10.2147/JPR.S112626

298 Hu J, Huang D, Li M, Wu C, Zhang J. Effects of a single dose of preoperative pregabalin and gabapentin for acute postoperative pain: a network meta-analysis of randomized controlled trials. Journal of Pain Research. doi:10.2147/JPR.S170810

299 Weinbroum AA, Gorodezky A, Niv D, Ben-Abraham R, Rudick V, Szold A. Dextromethorphan attenuation of postoperative pain and primary and secondary thermal hyperalgesia. Can J Anaesth. 2001;48(2):167. doi:10.1007/BF03019730

300 Weinbroum AA, Rudick V, Paret G, Ben-Abraham R. The role of dextromethorphan in pain control. Can J Anesth. 2000;47(6):585. doi:10.1007/BF03018952

301 Kurdi MS, Patel T. The role of melatonin in anaesthesia and critical care. Indian J Anaesth. 2013;57(2):137-144. doi:10.4103/0019-5049.111837

302 Mowafi H, Ismail S. The uses of melatonin in anesthesia and surgery. Saudi J Med Amp Med Sci. 2014;2(3):134-134.

303 Ambriz-Tututi M, Rocha-González HI, Cruz SL, Granados-Soto V. Melatonin: a hormone that modulates pain. Life Sci. 2009;84(15-16):489-498. doi:10.1016/j.lfs.2009.01.024

304 Wilhelmsen M, Amirian I, Reiter RJ, Rosenberg J, Gögenur I. Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies. J Pineal Res. 2011;51(3):270-277. doi:10.1111/j.1600-079X.2011.00895.x

305 Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR. Clonidine as an Adjuvant to Intrathecal Local Anesthetics for Surgery: Systematic Review of Randomized Trials. Reg Anesth Pain Med. 2008;33(2):159-167. doi:10.1016/j.rapm.2007.10.008

306 Samantaray A, Rao MH, Chandra A. The effect on post-operative pain of intravenous clonidine given before induction of anaesthesia. Indian J Anaesth. 2012;56(4):359. doi:10.4103/0019-5049.100817

307 Ahad S, Figueredo EJ. Laparoscopic Colectomy. Medscape Gen Med. 2007;9(2):37.

308 Cummings LC, Delaney CP, Cooper GS. Laparoscopic versus open colectomy for colon cancer in an older population: a cohort study. World J Surg Oncol. 2012;10(1):31. doi:10.1186/1477-7819-10-31

309 Lorenzon L, La Torre M, Ziparo V, et al. Evidence based medicine and surgical approaches for colon cancer: Evidences, benefits and limitations of the laparoscopic vs open resection. World J Gastroenterol WJG. 2014;20(13):3680-3692. doi:10.3748/wjg.v20.i13.3680

310 Hazebroek EJ, The Color Study Group. COLOR. Surg Endosc Interv Tech. 2002;16(6):949-953. doi:10.1007/s00464-001-8165-z

311 Ringressi MN, Boni L, Freschi G, et al. Comparing laparoscopic surgery with open surgery for long-term outcomes in patients with stage I to III colon cancer. Surg Oncol. 2018;27(2):115-122. doi:10.1016/j.suronc.2018.02.004

312 Lei Q-C, Wang X-Y, Zheng H-Z, et al. Laparoscopic Versus Open Colorectal Resection Within Fast Track Programs: An Update Meta-Analysis Based on Randomized Controlled Trials. J Clin Med Res. 2015;7(8):594-601. doi:10.14740/jocmr2177w

313 Joshi GP, Bonnet F, Kehlet H. Evidence-based postoperative pain management after laparoscopic colorectal surgery. Colorectal Dis. 2013;15(2):146-155. doi:10.1111/j.1463-1318.2012.03062.x

314 Bisgaard T, Klarskov B, Kehlet H, Rosenberg J. Preoperative Dexamethasone Improves Surgical Outcome After Laparoscopic Cholecystectomy. Ann Surg. 2003;238(5):651-660. doi:10.1097/01.sla.0000094390.82352.cb

315 Bakan M, Umutoglu T, Topuz U, et al. Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. Braz J Anesthesiol Engl Ed. 2015;65(3):191-199. doi:10.1016/j.bjane.2014.05.001

316 Guerra L, Philip S, Lax EA, Smithson L, Pearlman R, Damadi A. Transversus Abdominis Plane Blocks in Laparoscopic Colorectal Surgery: Better Pain Control and Patient Outcomes with Liposomal Bupivacaine than Bupivacaine. Am Surg. 2019;85(9):1013-1016.

317 Torgeson M, Kileny J, Pfeifer C, Narkiewicz L, Obi S. Conventional Epidural vs Transversus Abdominis Plane Block with Liposomal Bupivacaine: A Randomized Trial in Colorectal Surgery. J Am Coll Surg. 2018;227(1):78-83. doi:10.1016/j.jamcollsurg.2018.04.021

318 Stokes AL, Adhikary SD, Quintili A, et al. Liposomal Bupivacaine Use in Transversus Abdominis Plane Blocks Reduces Pain and Postoperative Intravenous Opioid Requirement After Colorectal Surgery. Dis Colon Rectum. 2017;60(2):170–177. doi:10.1097/DCR.0000000000000747

319 Elsharkawy H, El-Boghdadly K, Barrington M. Quadratus Lumborum Block: Anatomical Concepts, Mechanisms, and Techniques. Anesthesiology. 2019;130(2):322-335. doi:10.1097/ALN.0000000000002524

320 Jain K, Jaiswal V, Puri A. Erector spinae plane block: Relatively new block on horizon with a wide spectrum of application – A case series. Indian J Anaesth. 2018;62(10):809-813. doi:10.4103/ija.IJA_263_18

References continued

321 Kartalov A, Jankulovski N, Kuzmanovska B, et al. The Effect of Rectus Sheath Block as a Supplement of General Anesthesia on Postoperative Analgesia in Adult Patient Undergoing Umbilical Hernia Repair. Pril Makedon Akad Na Nauk Umet Oddelenie Za Med Nauki. 2017;38(3):135-142. doi:10.2478/prilozi-2018-0014

322 Hamilton TW, Athanassoglou V, Mellon S, et al. Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. Cochrane Database Syst Rev. 2017;2017(2). doi:10.1002/14651858.CD011419.pub2

323 Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. Curr Med Res Opin. 2012;28(10):1609-1615. doi:10.1185/03007995.2012.721760

324 Hamill JK, Rahiri J-L, Hill AG. Analgesic effect of intraperitoneal local anesthetic in surgery: an overview of systematic reviews. J Surg Res. 2017;212:167-177. doi:10.1016/j.jss.2017.01.022

325 Kahokehr A, Sammour T, Shoshtari KZ, Taylor M, Hill AG. Intraperitoneal Local Anesthetic Improves Recovery After Colon Resection: A Double-Blinded Randomized Controlled Trial. Ann Surg. 2011;254(1):28-38. doi:10.1097/SLA.0b013e318221f0cf

326 Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. BJS Br J Surg. 2008;95(11):1331-1338. doi:10.1002/bjs.6375

327 McCarthy GC, Megalla SA, Habib AS. Impact of Intravenous Lidocaine Infusion on Postoperative Analgesia and Recovery from Surgery. Drugs. 2010;70(9):1149-1163. doi:10.2165/10898560-000000000-00000

328 Vigneault L, Turgeon AF, Côté D, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anesth Can Anesth. 2011;58(1):22-37. doi:10.1007/s12630-010-9407-0

329 Dunn LK, Durieux ME. Perioperative Use of Intravenous Lidocaine: Anesthesiology. 2017;126(4):729-737. doi:10.1097/ALN.0000000000001527

330 Watts R, Thiruvenkatarajan V, Calvert M, Newcombe G, van Wijk RM. The effect of perioperative esmolol on early postoperative pain: A systematic review and meta-analysis. J Anaesthesiol Clin Pharmacol. 2017;33(1):28-39. doi:10.4103/0970-9185.202182

331 Gelineau AM, King MR, Ladha KS, Burns SM, Houle T, Anderson TA. Intraoperative Esmolol as an Adjunct for Perioperative Opioid and Postoperative Pain Reduction: A Systematic Review, Meta-analysis, and Meta-regression. doi:info:doi/10.1213/ANE.0000000000002469

332 De Oliveira GS, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative Systemic Magnesium to Minimize Postoperative Pain: A Meta-analysis of Randomized Controlled Trials. Anesthesiology. 2013;119(1):178-190. doi:10.1097/ALN.0b013e318297630d

333 Do S-H. Magnesium: a versatile drug for anesthesiologists. Korean J Anesthesiol. 2013;65(1):4-8. doi:10.4097/kjae.2013.65.1.4

334 Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anesth Can Anesth. 2011;58(10):911. doi:10.1007/s12630-011-9560-0

335 Elia N, Tramèr MR. Ketamine and postoperative pain – a quantitative systematic review of randomised trials. Pain. 2005;113(1):61-70. doi:10.1016/j.pain.2004.09.036

336 Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg. 2004;99(2):482-495, table of contents. doi:10.1213/01.ANE.0000118109.12855.07

337 Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists: Reg Anesth Pain Med. Published online June 2018:1. doi:10.1097/AAP.0000000000000806

338 Cheung CW, Qiu Q, Ying ACL, Choi SW, Law WL, Irwin MG. The effects of intra-operative dexmedetomidine on postoperative pain, side-effects and recovery in colorectal surgery. Anaesthesia. 2014;69(11):1214-1221. doi:10.1111/anae.12759

339 Grosu I, Lavand'homme P. Use of dexmedetomidine for pain control. F1000 Med Rep. 2010;2. doi:10.3410/M2-90

340 Grape S, Kirkham KR, Frauenknecht J, Albrecht E. Intra-operative analgesia with remifentanil vs. dexmedetomidine: a systematic review and meta-analysis with trial sequential analysis. Anaesthesia. 2019;74(6):793-800. doi:10.1111/anae.14657

341 Park J-K, Cheong SH, Lee KM, et al. Does dexmedetomidine reduce postoperative pain after laparoscopic cholecystectomy with multimodal analgesia? Korean J Anesthesiol. 2012;63(5):436-440. doi:10.4097/kjae.2012.63.5.436

342 Helander EM, Webb MP, Bias M, Whang EE, Kaye AD, Urman RD. Use of Regional Anesthesia Techniques: Analysis of Institutional Enhanced Recovery After Surgery Protocols for Colorectal Surgery. J Laparoendosc Adv Surg Tech. 2017;27(9):898-902. doi:10.1089/lap.2017.0339

343 Clarke HA, Katz J, McCartney CJL, et al. Perioperative gabapentin reduces 24 h opioid consumption and improves in-hospital rehabilitation but not post-discharge outcomes after total knee arthroplasty with peripheral nerve block. BJA Br J Anaesth. 2014;113(5):855-864. doi:10.1093/bja/aeu202

344 Alford DP, Compton P, Samet JH. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. Ann Intern Med. 2006;144(2):127-134.

345 Substance Abuse and Mental Health Services Administration. Special Circumstances for Providing Buprenorphine. Published 2016. https://www.samhsa.gov/medication-assisted-treatment/legislation-regulations-guidelines/speci l-circumstances-providing-buprenorphine.

346 Yousef AA, Salem HA, Moustafa MZ. Effect of mini-dose epidural dexmedetomidine in elective cesarean section using combined spinal-epidural anesthesia: a randomized double-blinded controlled study. J Anesth. 2015;29(5):708-714. doi:10.1007/s00540-015-2027-7

References continued

347 Behdad S, Hajiesmaeili MR, Abbasi HR, Ayatollahi V, Khadiv Z, Sedaghat A. Analgesic Effects of Intravenous Ketamine during Spinal Anesthesia in Pregnant Women Undergone Caesarean Section; A Randomized Clinical Trial. Anesthesiol Pain Med. 2013;3(2):230-233. doi:10.5812/aapm.7034

348 Society of Obstetric Anesthesia and Perinatology (SOAP) Enhanced Recovery After Cesarean (ERAC) Consensus Statement. Published May 23, 2019. Accessed July 24, 2020. https://soap.org/SOAP-Enhanced-Recovery-After-Cesarean-Consensus-Statement.pdf

349 Peters AA, van Dorst E, Jellis B, van Zuuren E, Hermans J, Trimbos JB. A randomized clinical trial to compare two different approaches in women with chronic pelvic pain. Obstet Gynecol. 1991;77(5):740-744.

350 Savidge CJ, Slade P. Psychological aspects of chronic pelvic pain. J Psychosom Res. 1997;42(5):433-444. doi:10.1016/S0022-3999(96)00300-5

351 Latthe P, Mignini L, Gray R, Hills R, Khan K. Factors predisposing women to chronic pelvic pain: systematic review. BMJ. 2006;332(7544):749-755. doi:10.1136/bmj.38748.697465.55

352 Allegrante JP. The role of adjunctive therapy in the management of chronic nonmalignant pain. Am J Med. 1996;101:S33-S39. doi:10.1016/S0002-9343(96)00136-2

353 Cheong YC, Smotra G, Williams AC de C. Non-surgical interventions for the management of chronic pelvic pain. Cochrane Database Syst Rev. 2014;(3). doi:10.1002/14651858.CD008797.pub2

354 Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain. 1999;80(1):1-13. doi:10.1016/S0304-3959(98)00255-3

355 Fox SD, Flynn E, Allen RH. Mindfulness meditation for women with chronic pelvic pain: a pilot study. J Reprod Med. 2011;56(3-4):158-162.

356 Xu Y, Zhao W, Li T, Zhao Y, Bu H, Song S. Effects of acupuncture for the treatment of endometriosis-related pain: A systematic review and meta-analysis. PloS One. 2017;12(10):e0186616. doi:10.1371/journal.pone.0186616

357 Huang AJ, Rowen TS, Abercrombie P, et al. Development and Feasibility of a Group-Based Therapeutic Yoga Program for Women with Chronic Pelvic Pain. Pain Med Malden Mass. 2017;18(10):1864-1872. doi:10.1093/pm/pnw306

358 Zoorob D, South M, Karram M, et al. A pilot randomized trial of levator injections versus physical therapy for treatment of pelvic floor myalgia and sexual pain. Int Urogynecology J. 2015;26(6):845-852. doi:10.1007/s00192-014-2606-4

359 Polackwich Alan Scott, Li Jianbo, Shoskes Daniel A. Patients with Pelvic Floor Muscle Spasm Have a Superior Response to Pelvic Floor Physical Therapy at Specialized Centers. J Urol. 2015;194(4):1002-1006. doi:10.1016/j.juro.2015.03.130

360 Slocumb JC. Neurological factors in chronic pelvic pain: Trigger points and the abdominal pelvic pain syndrome. Am J Obstet Gynecol. 1984;149(5):536-543. doi:10.1016/0002-9378(84)90032-2

361 Tam J, Loeb C, Grajower D, Kim J, Weissbart S. Neuromodulation for Chronic Pelvic Pain. Curr Urol Rep. 2018;19(5):32. doi:10.1007/s11934-018-0783-2

362 Sharma N, Rekha K, Srinivasan JK. Efficacy of transcutaneous electrical nerve stimulation in the treatment of chronic pelvic pain. J -Life Health. 2017;8(1):36-39. doi:10.4103/jmh.JMH_60_16

363 Weijenborg PTM, Greeven A, Dekker FW, Peters AAW, ter Kuile MM. Clinical course of chronic pelvic pain in women. PAIN. 2007;132:S117-S123. doi:10.1016/j.pain.2007.06.020

364 Poterucha TJ, Murphy SL, Rho RH, et al. Topical Amitriptyline-Ketamine for Treatment of Rectal, Genital, and Perineal Pain and Discomfort. Pain Physician.:4.

365 Steege JF, Siedhoff MT. Chronic Pelvic Pain. Obstet Gynecol. 2014;124(3):616–629. doi:10.1097/AOG.0000000000000417

366 Lewis SC, Bhattacharya S, Wu O, et al. Gabapentin for the Management of Chronic Pelvic Pain in Women (GaPP1): A Pilot Randomised Controlled Trial. PloS One. 2016;11(4):e0153037. doi:10.1371/journal.pone.0153037

367 Taylor HS, Giudice LC, Lessey BA, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. N Engl J Med. 2017;377(1):28-40. doi:10.1056/NEJMoa1700089

368 Surrey E, Taylor HS, Giudice L, et al. Long-Term Outcomes of Elagolix in Women With Endometriosis: Results From Two Extension Studies. Obstet Gynecol. 2018;132(1):147-160. doi:10.1097/AOG.0000000000002675

369 De Andres J, Sanchis-Lopez N, Asensio-Samper JM, et al. Vulvodynia--An Evidence-Based Literature Review and Proposed Treatment Algorithm. Pain Pract Off J World Inst Pain. 2016;16(2):204-236. doi:10.1111/papr.12274

370 American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice, American Society for Colposcopy and Cervical Pathology (ASCCP). Committee Opinion No 673: Persistent Vulvar Pain. Obstet Gynecol. 2016;128(3):e78-84. doi:10.1097/AOG.0000000000001645

371 Andrews JC. Vulvodynia: An evidence-based approach to medical management. J Clin Outcomes Manag. 2010;17:38-56.

372 Andrews JC. Vulvodynia interventions--systematic review and evidence grading. Obstet Gynecol Surv. 2011;66(5):299-315. doi:10.1097/OGX.0b013e3182277fb7

373 Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. J Low Genit Tract Dis. 2005;9(1):40-51. doi:10.1097/00128360-200501000-00009

374 Lifits-Podorozhansky YM, Podorozhansky Y, Hoffstetter S, Gavard JA. Role of vulvar care guidelines in the initial management of vulvar complaints. J Low Genit Tract Dis. 2012;16(2):88-91. doi:10.1097/LGT.0b013e318232fd9a

References continued

375 Mandal D, Nunns D, Byrne M, et al. Guidelines for the management of vulvodynia. Br J Dermatol. 2010;162(6):1180-1185. doi:10.1111/j.1365-2133.2010.09684.x

376 Reed BD. Vulvodynia: diagnosis and management. Am Fam Physician. 2006;73(7):1231-1238.

377 Meltzer-Brody SE, Zolnoun D, Steege JF, Rinaldi KL, Leserman J. Open-label trial of lamotrigine focusing on efficacy in vulvodynia. J Reprod Med. 2009;54(3):171-178.

378 Tu FF, Hellman KM, Backonja MM. Gynecologic management of neuropathic pain. Am J Obstet Gynecol. 2011;205(5):435-443. doi:10.1016/j.ajog.2011.05.011

379 Brown C, Bachmann G, Foster D, Rawlinson L, Wan J, Ling F. Milnacipran in provoked vestibulodynia: efficacy and predictors of treatment success. J Low Genit Tract Dis. 2015;19(2):140-144. doi:10.1097/LGT.0000000000000057

380 Weinschenk S, Brocker K, Hotz L, Strowitzki T, Joos S, HUNTER (Heidelberg University Neural Therapy Education and Research) Group. Successful therapy of vulvodynia with local anesthetics: a case report. Forsch Komplementarmedizin 2006. 2013;20(2):138-143. doi:10.1159/000350023

381 Armour M, Ee CC, Naidoo D, et al. Exercise for dysmenorrhoea. Cochrane Database Syst Rev. 2019;9:CD004142. doi:10.1002/14651858.CD004142.pub4

382 Matthewman G, Lee A, Kaur JG, Daley AJ. Physical activity for primary dysmenorrhea: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol. 2018;219(3):255.e1-255.e20. doi:10.1016/j.ajog.2018.04.001

383 Akin MD, Weingand KW, Hengehold DA, Goodale MB, Hinkle RT, Smith RP. Continuous low-level topical heat in the treatment of dysmenorrhea. Obstet Gynecol. 2001;97(3):343-349. doi:10.1016/s0029-7844(00)01163-7

384 Burnett M, Lemyre M. No. 345-Primary Dysmenorrhea Consensus Guideline. J Obstet Gynaecol Can JOGC J Obstet Gynecol Can JOGC. 2017;39(7):585-595. doi:10.1016/j.jogc.2016.12.023

385 Proctor ML, Smith CA, Farquhar CM, Stones RW. Transcutaneous electrical nerve stimulation and acupuncture for primary dysmenorrhoea. Cochrane Database Syst Rev. 2002;(1):CD002123. doi:10.1002/14651858.CD002123

386 Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database Syst Rev. 2015;(7):CD001751. doi:10.1002/14651858.CD001751.pub3

387 Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhea. Am Fam Physician. 2014;89(5):341-346.

388 Ali Z, Burnett I, Eccles R, et al. Efficacy of a paracetamol and caffeine combination in the treatment of the key symptoms of primary dysmenorrhoea. Curr Med Res Opin. 2007;23(4):841-851. doi:10.1185/030079907x182239

389 Sugumar R, Krishnaiah V, Channaveera GS, Mruthyunjaya S. Comparison of the pattern, efficacy, and tolerability of self-medicated drugs in primary dysmenorrhea: a questionnaire based survey. Indian J Pharmacol. 2013;45(2):180-183. doi:10.4103/0253-7613.108312

390 Saei Ghare Naz M, Kiani Z, Rashidi Fakari F, Ghasemi V, Abed M, Ozgoli G. The Effect of Micronutrients on Pain Management of Primary Dysmenorrhea: a Systematic Review and Meta-Analysis. J Caring Sci. 2020;9(1):47-56. doi:10.34172/jcs.2020.008

391 Bahrami A, Avan A, Sadeghnia HR, et al. High dose vitamin D supplementation can improve menstrual problems, dysmenorrhea, and premenstrual syndrome in adolescents. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2018;34(8):659-663. doi:10.1080/09513590.2017.1423466

392 Sadeghi N, Paknezhad F, Rashidi Nooshabadi M, Kavianpour M, Jafari Rad S, Khadem Haghighian H. Vitamin E and fish oil, separately or in combination, on treatment of primary dysmenorrhea: a double-blind, randomized clinical trial. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2018;34(9):804-808. doi:10.1080/09513590.2018.1450377

393 Kashanian M, Lakeh MM, Ghasemi A, Noori S. Evaluation of the effect of vitamin E on pelvic pain reduction in women suffering from primary dysmenorrhea. J Reprod Med. 2013;58(1-2):34-38.

394 Nayeban S, Jafarnejad F, Nayeban S, Sefidgaran A. A Comparison of the Effects of Vitamin E and Vitamin B1 on the Severity and Duration of Pain in Primary Dysmenorrhea. J Midwifery Reprod Health. 2014;2(2):143-146. doi:10.22038/jmrh.2014.2397

395 Bokaie M, Farajkhoda T, Enjezab B, Khoshbin A, Karimi-Zarchi M, Zarchi Mojgan K. Oral fennel (Foeniculum vulgare) drop effect on primary dysmenorrhea: Effectiveness of herbal drug. Iran J Nurs Midwifery Res. 2013;18(2):128-132.

396 Nazari M, Rostami-Moez M, Ebrahimi F. The Effect of Fennel on Pain Relief in Primary Dysmenorrhea: A Systematic Review of Clinical Trials. Int J Epidemiol Res. 2020;7(1):44-48. doi:10.34172/ijer.2020.08

397 Pattanittum P, Kunyanone N, Brown J, et al. Dietary supplements for dysmenorrhoea. Cochrane Database Syst Rev. 2016;3:CD002124. doi:10.1002/14651858.CD002124.pub2

398 Zhang X, Zhang R, Chen D, et al. Association of tea drinking and dysmenorrhoea among reproductive-age women in Shanghai, China (2013–2015): a cross-sectional study. BMJ Open. 2019;9(4). doi:10.1136/bmjopen-2018-026643

399 Imperial College London. Ovarian cysts should be “watched” rather than removed, study suggests. ScienceDaily. Published February 5, 2019. Accessed July 28, 2020. https://www.sciencedaily.com/releases/2019/02/190205185156.htm

400 American College of Obstetricians and Gynecologists’ Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol. 2018;132(5):e197-e207. doi:10.1097/AOG.0000000000002899

401 Simkin PP, O’hara M. Nonpharmacologic relief of pain during labor: systematic reviews of five methods. Am J Obstet Gynecol. 2002;186(5 Suppl Nature):S131-159. doi:10.1067/mob.2002.122382

402 Benfield RD, Hortobágyi T, Tanner CJ, Swanson M, Heitkemper MM, Newton ER. The effects of hydrotherapy on anxiety, pain, neuroendocrine responses, and contraction dynamics during labor. Biol Res Nurs. 2010;12(1):28-36. doi:10.1177/1099800410361535

References continued

403 Pawelec M, Pietras J, Wojtysiak M, et al. Water birth and water immersion - An important step towards more patient-oriented health care or a new way for obstetrical wards to make profits? Adv Clin Exp Med. 2011;20:391-397.
404 Smith CA, Collins CT, Cyna AM, Crowther CA. Complementary and alternative therapies for pain management in labour. Cochrane Database Syst Rev. 2003;(2):CD003521. doi:10.1002/14651858.CD003521
405 Santana LS, Gallo RBS, Ferreira CHJ, Duarte G, Quintana SM, Marcolin AC. Transcutaneous electrical nerve stimulation (TENS) reduces pain and postpones the need for pharmacological analgesia during labour: a randomised trial. J Physiother. 2016;62(1):29-34. doi:10.1016/j.jphys.2015.11.002
406 Mello LFD, Nóbrega LF, Lemos A. Transcutaneous electrical stimulation for pain relief during labor: a systematic review and meta-analysis. Rev Bras Fisioter Sao Carlos Sao Paulo Braz. 2011;15(3):175-184.
407 Czech I, Fuchs P, Fuchs A, et al. Pharmacological and Non-Pharmacological Methods of Labour Pain Relief-Establishment of Effectiveness and Comparison. Int J Environ Res Public Health. 2018;15(12). doi:10.3390/ijerph15122792
408 Howell CJ. Epidural versus non-epidural analgesia for pain relief in labour. Cochrane Database Syst Rev. 2000;(2):CD000331. doi:10.1002/14651858.CD000331
409 Freeman LM, Bloemenkamp KWM, Franssen MTM, et al. Remifentanil patient controlled analgesia versus epidural analgesia in labour. A multicentre randomized controlled trial. BMC Pregnancy Childbirth. 2012;12:63. doi:10.1186/1471-2393-12-63
410 George RB, Allen TK, Habib AS. Intermittent Epidural Bolus Compared with Continuous Epidural Infusions for Labor Analgesia: A Systematic Review and Meta-Analysis. Anesth Analg. 2013;116(1):133–144. doi:10.1213/ANE.0b013e3182713b26
411 Likis FE, Andrews JC, Collins MR, et al. Nitrous oxide for the management of labor pain: a systematic review. Anesth Analg. 2014;118(1):153-167. doi:10.1213/ANE.0b013e3182a7f73c
412 Koyyalamudi V, Sidhu G, Cornett EM, et al. New Labor Pain Treatment Options. Curr Pain Headache Rep. 2016;20(2):11. doi:10.1007/s11916-016-0543-2
413 East CE, Begg L, Henshall NE, Marchant PR, Wallace K. Local cooling for relieving pain from perineal trauma sustained during childbirth. Cochrane Database Syst Rev. 2012;(5). doi:10.1002/14651858.CD006304.pub3
414 Dennis C-L, Jackson K, Watson J. Interventions for treating painful nipples among breastfeeding women. Cochrane Database Syst Rev. 2014;(12). doi:10.1002/14651858.CD007366.pub2
415 Berens P, Eglash A, Malloy M, Steube AM. ABM Clinical Protocol #26: Persistent Pain with Breastfeeding. Breastfeed Med. 2016;11(2):46-53. doi:10.1089/bfm.2016.29002.pjb
416 Vieira F, Mota DDCF, Castral TC, Guimarães JV, Salge AKM, Bachion MM. Effects of Anhydrous Lanolin versus Breast Milk Combined with a Breast Shell for the Treatment of Nipple Trauma and Pain During Breastfeeding: A Randomized Clinical Trial. J Midwifery Womens Health. 2017;62(5):572-579. doi:10.1111/jmwh.12644
417 Soares A, Andriolo RB, Atallah AN, da Silva EMK. Botulinum toxin for myofascial pain syndromes in adults. Cochrane Database Syst Rev. 2014;(7):CD007533. doi:10.1002/14651858.CD007533.pub3
418 Abbott J. Gynecological indications for the use of botulinum toxin in women with chronic pelvic pain. Toxicon Off J Int Soc Toxinology. 2009;54(5):647-653. doi:10.1016/j.toxicon.2009.01.036
419 Briggs GG, Freeman RK, Towers CV, Forinash AB. Drugs in Pregnancy and Lactation. Lippincott Williams & Wilkins; 2016.
420 Jun G-W, Kim M-S, Yang H-J, et al. Laparoscopic appendectomy under spinal anesthesia with dexmedetomidine infusion. Korean J Anesthesiol. 2014;67(4):246-251. doi:10.4097/kjae.2014.67.4.246
421 Andersen JH, Jaeger P, Grevstad U, et al. Systemic dexmedetomidine is not as efficient as perineural dexmedetomidine in prolonging an ulnar nerve block. Reg Anesth Pain Med. 2019;44(3):333-340. doi:10.1136/rapm-2018-100089
422 Hedayati H, Parsons J, Crowther CA. Topically applied anaesthetics for treating perineal pain after childbirth. Cochrane Database Syst Rev. 2005;(2). doi:10.1002/14651858.CD004223.pub2
423 Kaewjiaranai T, Srisatjaluk RL, Sakdajeyont W, Pairuchvej V, Wongsirichat N. The efficiency of topical anesthetics as antimicrobial agents: A review of use in dentistry. J Dent Anesth Pain Med. 2018;18(4):223-233. doi:10.17245/jdapm.2018.18.4.223
424 Johnson SM, Saint John BE, Dine AP. Local anesthetics as antimicrobial agents: a review. Surg Infect. 2008;9(2):205-213. doi:10.1089/sur.2007.036
425 Oor JE, Ünlü Ç, Hazebroek EJ. A systematic review of the treatment for abdominal cutaneous nerve entrapment syndrome. Am J Surg. 2016;212(1):165-174. doi:10.1016/j.amjsurg.2015.12.013
426 Montenegro MLLS, Braz CA, Rosa-e-Silva JC, Candido-dos-Reis FJ, Nogueira AA, Poli-Neto OB. Anaesthetic injection versus ischemic compression for the pain relief of abdominal wall trigger points in women with chronic pelvic pain. BMC Anesthesiol. 2015;15:175. doi:10.1186/s12871-015-0155-0
427 Scott NA, Guo B, Barton PM, Gerwin RD. Trigger point injections for chronic non-malignant musculoskeletal pain: a systematic review. Pain Med Malden Mass. 2009;10(1):54-69. doi:10.1111/j.1526-4637.2008.00526.x
428 Fouad LS, Chen AH, Pettit PD, Micallef A. Transvaginal Trigger Point Injections for Pelvic Floor Myofascial Spasm: A Retrospective Review of Pain Assessment and Development of a Treatment Algorithm. J Minim Invasive Gynecol. 2015;22(6S):S247-S248. doi:10.1016/j.jmig.2015.08.864
429 McDonald JS, Rapkin AJ. Multilevel local anesthetic nerve blockade for the treatment of generalized vulvodynia: a pilot study. J Sex Med. 2012;9(11):2919-2926. doi:10.1111/j.1743-6109.2012.02909.x
430 Kainu JP, Sarvela J, Halonen P, et al. Continuous wound infusion with ropivacaine fails to provide adequate analgesia after caesarean section. Int J Obstet Anesth. 2012;21(2):119-124. doi:10.1016/j.ijoa.2011.12.009

References continued

431 Barney E. Wound Infusion with the On-q Pump for Analgesia after Cesarean Delivery: A Randomized, Double-blind, Placebo-controlled Trial. The Anesthesiology Annual Meeting. Published October 19, 2019. Accessed July 31, 2020. http://www.asaabstracts.com/strands/asaabstracts/abstract.htm?year=2019&index=14&absnum=1713

432 Rackelboom T, Le Strat S, Silvera S, et al. Improving continuous wound infusion effectiveness for postoperative analgesia after cesarean delivery: a randomized controlled trial. Obstet Gynecol. 2010;116(4):893-900. doi:10.1097/AOG.0b013e3181f38ac6

433 Givens VA, Lipscomb GH, Meyer NL. A randomized trial of postoperative wound irrigation with local anesthetic for pain after cesarean delivery. Am J Obstet Gynecol. 2002;186(6):1188-1191. doi:10.1067/mob.2002.122984

434 Zaretsky M, Wood C, Nivens T, et al. Continuous local bupivacaine wound infusion with neuraxial morphine reduces opioid consumption after cesarean delivery. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2019;32(23):3895-3902. doi:10.1080/14767058.2018.1474872

435 ELShamaa HA, Ibrahim M. Bupivacaine constant continuous surgical wound infusion versus continuous epidural infusion for post cesarean section pain, randomized placebo-controlled study. Egypt J Anaesth. 2016;32(4):541-547. doi:10.1016/j.egja.2016.08.017

436 Adesope O, Ituk U, Habib AS. Local anaesthetic wound infiltration for postcaesarean section analgesia: A systematic review and meta-analysis. Eur J Anaesthesiol. 2016;33(10):731-742. doi:10.1097/EJA.0000000000000462

437 MacFater WS, Xia W, Barazanchi A, Su'a B, Svirskis D, Hill AG. Intravenous Local Anaesthetic Compared with Intraperitoneal Local Anaesthetic in Abdominal Surgery: A Systematic Review. World J Surg. 2018;42(10):3112-3119. doi:10.1007/s00268-018-4623-9

438 Sammour T, Kahokehr A, Soop M, Hill AG. Peritoneal Damage: The Inflammatory Response and Clinical Implications of the Neuro-Immuno-Humoral Axis. World J Surg. 2010;34(4):704-720. doi:10.1007/s00268-009-0382-y

439 Cervero F. Visceral versus Somatic Pain: Similarities and Differences. Dig Dis. 2009;27(Suppl. 1):3-10. doi:10.1159/000268115

440 Perniola A, Fant F, Magnuson A, Axelsson K, Gupta A. Postoperative pain after abdominal hysterectomy: a randomized, double-blind, controlled trial comparing continuous infusion vs patient-controlled intraperitoneal injection of local anaesthetic. BJA Br J Anaesth. 2014;112(2):328-336. doi:10.1093/bja/aet345

441 Perniola A, Magnuson A, Axelsson K, Gupta A. Intraperitoneal Local Anesthetics Have Predominant Local Analgesic Effect: A Randomized, Double-blind Study. Surv Anesthesiol. 2015;59(3):152–153. doi:10.1097/01.sa.0000464132.89889.dc

442 Patel SD, Sharawi N, Sultan P. Local anaesthetic techniques for post-caesarean delivery analgesia. Int J Obstet Anesth. 2019;40:62-77. doi:10.1016/j.ijoa.2019.06.002

443 Kahokehr DA, Sammour T, Vather R, Taylor M, Stapelberg F, Hill AG. Systemic Levels of Local Anaesthetic after Intra-Peritoneal Application – a Systematic Review: Anaesth Intensive Care. Published online July 1, 2010. doi:10.1177/0310057X1003800404

444 Gholipour Baradari A, Firouzian A, Hasanzadeh Kiabi F, et al. Bolus administration of intravenous lidocaine reduces pain after an elective caesarean section: Findings from a randomised, double-blind, placebo-controlled trial. J Obstet Gynaecol J Inst Obstet Gynaecol. 2017;37(5):566-570. doi:10.1080/01443615.2016.1264071

445 El-Tahan MR, Warda OM, Diab DG, Ramzy EA, Matter MK. A randomized study of the effects of perioperative i.v. lidocaine on hemodynamic and hormonal responses for cesarean section. J Anesth. 2009;23(2):215-221. doi:10.1007/s00540-009-0738-3

446 Samimi S, Taheri A, Davari Tanha F. Comparison Between Intraperitoneal and Intravenous Lidocaine for Postoperative Analgesia After Elective Abdominal Hysterectomy, a Double-Blind Placebo Controlled Study. J Fam Reprod Health. 2015;9(4):193-198.

447 Wang H-L, Yan H-D, Liu Y-Y, et al. Intraoperative intravenous lidocaine exerts a protective effect on cell-mediated immunity in patients undergoing radical hysterectomy. Mol Med Rep. 2015;12(5):7039-7044. doi:10.3892/mmr.2015.4235

448 Lau LL, Li CY, Lee A, Chan SK. The use of 5% lidocaine medicated plaster for acute postoperative pain after gynecological surgery: A pilot randomized controlled feasibility trial. Medicine (Baltimore). 2018;97(39):e12582. doi:10.1097/MD.0000000000012582

449 Kim JE, Kim JY, Lee HS, Seok S, Kil HK. Analgesic effect of trigger point injection and EMLA for shoulder pain in patients undergoing total laparoscopic hysterectomy: A randomized controlled study. Medicine (Baltimore). 2019;98(2):e14087. doi:10.1097/MD.0000000000014087

450 Ton R, Stovall DW, Rhoades-Lazenby C. The Effects of Infiltration of Liposomal Bupivacaine for Pain Control After Cesarean Delivery: A Randomized Trial [19T]. Obstet Gynecol. 2019;133:218S. doi:10.1097/01.AOG.0000559121.37433.42

451 Hutchins J, Argenta P, Berg A, Habeck J, Kaizer A, Geller MA. Ultrasound-guided subcostal transversus abdominis plane block with liposomal bupivacaine compared to bupivacaine infiltration for patients undergoing robotic-assisted and laparoscopic hysterectomy: a prospective randomized study. J Pain Res. 2019;12:2087-2094. doi:10.2147/JPR.S193872

452 Prabhu M, Clapp MA, McQuaid-Hanson E, et al. Liposomal Bupivacaine Block at the Time of Cesarean Delivery to Decrease Postoperative Pain: A Randomized Controlled Trial. Obstet Gynecol. 2018;132(1):70-78. doi:10.1097/AOG.0000000000002649

453 Kindig M, Mouch A, Adams D, Maxwell R, Yaklic J. Liposomal Bupivacaine Decreases Pain Scores and Narcotic Use After Cesarean Delivery [19E]. Obstet Gynecol. 2020;135:54S. doi:10.1097/01.AOG.0000663416.61377.3c

454 Parikh P, Sunesara I, Singh Multani S, Patterson B, Lutz E, Martin JN. Intra-incisional liposomal bupivacaine and its impact on postcesarean analgesia: a retrospective study. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2019;32(6):966-970. doi:10.1080/14767058.2017.1397118

455 Pacira BioSciences, Inc. Clinical and economic value outcomes with EXPAREL. Published 2020. Accessed January 7, 2020. https://www.exparel.com/hcp/cost

456 Hadzic A, Abikhaled JA, Harmon WJ. Impact of volume expansion on the efficacy and pharmacokinetics of liposome bupivacaine. Local Reg Anesth. 2015;8:105-111. doi:10.2147/LRA.S88685

References continued

457 Neal JM, Barrington MJ, Fettiplace MR, et al. The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity: Executive Summary 2017. Reg Anesth Pain Med. 2018;43(2):113-123. doi:10.1097/AAP.0000000000000720

458 Gitman M, Fettiplace MR, Weinberg GL, Neal JM, Barrington MJ. Local Anesthetic Systemic Toxicity: A Narrative Literature Review and Clinical Update on Prevention, Diagnosis, and Management. Plast Reconstr Surg. 2019;144(3):783-795. doi:10.1097/PRS.0000000000005989

459 Christie LE, Picard J, Weinberg GL. Local anaesthetic systemic toxicity. BJA Educ. 2015;15(3):136-142. doi:10.1093/bjaceaccp/mku027

460 Bern S, Weinberg G. Local anesthetic toxicity and lipid resuscitation in pregnancy. Curr Opin Anaesthesiol. 2011;24(3):262-267. doi:10.1097/ACO.0b013e32834654df

461 Engeler D, Baranowski AP. EAU Guidelines: Chronic Pelvic Pain. Uroweb. Accessed July 30, 2020. https://uroweb.org/guideline/chronic-pelvic-pain/

462 Speer L, Mushkbar S, Erbele T. Chronic Pelvic Pain in Women. Am Fam Physician. 2016;93(5):380-387.

463 Sator-Katzenschlager SM, Scharbert G, Kress HG, et al. Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. Wien Klin Wochenschr. 2005;117(21-22):761-768. doi:10.1007/s00508-005-0464-2

464 Munday PE. Response to treatment in dysaesthetic vulvodynia. J Obstet Gynaecol J Inst Obstet Gynaecol. 2001;21(6):610-613. doi:10.1080/01443610120085591

465 Leo RJ, Dewani S. A systematic review of the utility of antidepressant pharmacotherapy in the treatment of vulvodynia pain. J Sex Med. 2013;10(10):2497-2505. doi:10.1111/j.1743-6109.2012.02915.x

466 Spoelstra SK, Borg C, Weijmar Schultz WCM. Anticonvulsant pharmacotherapy for generalized and localized vulvodynia: a critical review of the literature. J Psychosom Obstet Gynaecol. 2013;34(3):133-138. doi:10.3109/0167482X.2013.823942

467 Ben-David B, Friedman M. Gabapentin therapy for vulvodynia. Anesth Analg. 1999;89(6):1459-1460. doi:10.1097/00000539-199912000-00026

468 Zorrilla-Vaca A, Stone A, Caballero-Lozada AF, Paredes S, Grant MC. Perioperative duloxetine for acute postoperative analgesia: a meta-analysis of randomized trials. Reg Anesth Pain Med. Published online August 1, 2019. doi:10.1136/rapm-2019-100687

469 Castro-Alves LJ, Oliveira de Medeiros ACP, Neves SP, et al. Perioperative Duloxetine to Improve Postoperative Recovery After Abdominal Hysterectomy: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Study. Anesth Analg. 2016;122(1):98-104. doi:10.1213/ANE.0000000000000971

470 Kain ZN, Sevarino FB, Rinder C, et al. Preoperative anxiolysis and postoperative recovery in women undergoing abdominal hysterectomy. Anesthesiology. 2001;94(3):415-422. doi:10.1097/00000542-200103000-00009

471 Caumo W, Hidalgo MPL, Schmidt AP, et al. Effect of pre-operative anxiolysis on postoperative pain response in patients undergoing total abdominal hysterectomy. Anaesthesia. 2002;57(8):740-746. doi:10.1046/j.1365-2044.2002.02690.x

472 Mijderwijk H, van Beek S, Klimek M, Duivenvoorden HJ, Grüne F, Stolker RJ. Lorazepam does not improve the quality of recovery in day-case surgery patients: a randomised placebo-controlled clinical trial. Eur J Anaesthesiol. 2013;30(12):743-751. doi:10.1097/EJA.0b013e328361d395

473 Maurice-Szamburski A, Auquier P, Viarre-Oreal V, et al. Effect of sedative premedication on patient experience after general anesthesia: a randomized clinical trial. JAMA. 2015;313(9):916-925. doi:10.1001/jama.2015.1108

474 Perry F, Parker RK, White PF, Clifford PA. Role of psychological factors in postoperative pain control and recovery with patient-controlled analgesia. Clin J Pain. 1994;10(1):57-63; discussion 82-85. doi:10.1097/00002508-199403000-00008

475 Caumo W, Schmidt AP, Schneider CN, et al. Risk factors for postoperative anxiety in adults. Anaesthesia. 2001;56(8):720-728. doi:10.1046/j.1365-2044.2001.01842.x

476 Hidalgo MPL, Auzani JAS, Rumpel LC, Moreira NL, Cursino AWC, Caumo W. The clinical effect of small oral clonidine doses on perioperative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg. 2005;100(3):795-802, table of contents. doi:10.1213/01.ANE.0000143568.59766.B2

477 Majumdar S, Das A, Das H, Bandyopadhyay S, Hajra BK, Mukherjee D. Comparative evaluation of oral gabapentin versus clonidine as premedication on preoperative sedation and laryngoscopic stress response attenuation for the patients undergoing general anesthesia. Perspect Clin Res. 2015;6(4):211-216. doi:10.4103/2229-3485.167094

478 AbdelHafeez MA, Reda A, Elnaggar A, EL-Zeneiny H, Mokhles JM. Gabapentin for the management of chronic pelvic pain in women. Arch Gynecol Obstet. 2019;300(5):1271-1277. doi:10.1007/s00404-019-05272-z

479 Clarke H, Kirkham KR, Orser BA, et al. Gabapentin reduces preoperative anxiety and pain catastrophizing in highly anxious patients prior to major surgery: a blinded randomized placebo-controlled trial. Can J Anaesth J Can Anesth. 2013;60(5):432-443. doi:10.1007/s12630-013-9890-1

480 Tirault M, Foucan L, Debaene B, et al. Gabapentin premedication: assessment of preoperative anxiolysis and postoperative patient satisfaction. Acta Anaesthesiol Belg. 2010;61(4):203-209.

481 Caumo W, Levandovski R, Hidalgo MPL. Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double-blind, randomized, placebo-controlled study. J Pain Off J Am Pain Soc. 2009;10(1):100-108. doi:10.1016/j.jpain.2008.08.007

482 Huang F, Yang Z, Li C-Q. The Melatonergic System in Anxiety Disorders and the Role of Melatonin in Conditional Fear. Vitam Horm. 2017;103:281-294. doi:10.1016/bs.vh.2016.09.003

References continued

483 Chia YY, Chan MH, Ko NH, Liu K. Role of beta-blockade in anaesthesia and postoperative pain management after hysterectomy. Br J Anaesth. 2004;93(6):799-805. doi:10.1093/bja/aeh268

484 Kerai S, Saxena KN, Taneja B. Post-caesarean analgesia: What is new? Indian J Anaesth. 2017;61(3):200-214. doi:10.4103/ija.IJA_313_16

485 Ortiz MI, Murguía-Cánovas G, Vargas-López LC, Silva R, González-de la Parra M. Naproxen, paracetamol and pamabrom versus paracetamol, pyrilamine and pamabrom in primary dysmenorrhea: a randomized, double-blind clinical trial. Medwave. 2016;16(9):e6587. doi:10.5867/medwave.2016.09.6587

486 Derry CJ, Derry S, Moore RA. Caffeine as an analgesic adjuvant for acute pain in adults. Cochrane Database Syst Rev. 2014;(12):CD009281. doi:10.1002/14651858.CD009281.pub3

487 Chandok N, Watt KDS. Pain Management in the Cirrhotic Patient: The Clinical Challenge. Mayo Clin Proc. 2010;85(5):451-458. doi:10.4065/mcp.2009.0534

488 Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. J Crit Care. 2010;25(3):458-462. doi:10.1016/j.jcrc.2009.12.012

489 Aryaie AH, Lalezari S, Sergent WK, et al. Decreased opioid consumption and enhance recovery with the addition of IV Acetaminophen in colorectal patients: a prospective, multi-institutional, randomized, double-blinded, placebo-controlled study (DOCIVA study). Surg Endosc. 2018;32(8):3432-3438. doi:10.1007/s00464-018-6062-y

490 Smith HS. Perioperative intravenous acetaminophen and NSAIDs. Pain Med Malden Mass. 2011;12(6):961-981. doi:10.1111/j.1526-4637.2011.01141.x

491 Macario A, Royal MA. A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. Pain Pract Off J World Inst Pain. 2011;11(3):290-296. doi:10.1111/j.1533-2500.2010.00426.x

492 Towheed T, Maxwell L, Judd M, Catton M, Hochberg MC, Wells GA. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev. 2006;(1). doi:10.1002/14651858.CD004257.pub2

493 Akhavanakbari G, Entezariasl M, Isazadehfar K, Kahnamoyiagdam F. The effects of indomethacin, diclofenac, and acetaminophen suppository on pain and opioids consumption after cesarean section. Perspect Clin Res. 2013;4(2):136-141. doi:10.4103/2229-3485.111798

494 Mitra S, Khandelwal P, Sehgal A. Diclofenac-tramadol vs. diclofenac-acetaminophen combinations for pain relief after caesarean section. Acta Anaesthesiol Scand. 2012;56(6):706-711. doi:10.1111/j.1399-6576.2012.02663.x

495 Jibril F, Sharaby S, Mohamed A, Wilby KJ. Intravenous versus Oral Acetaminophen for Pain: Systematic Review of Current Evidence to Support Clinical Decision-Making. Can J Hosp Pharm. 2015;68(3):238-247.

496 Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2011;(3):CD007938. doi:10.1002/14651858.CD007938.pub2

497 Agarwal MM, Elsi Sy M. Gabapentenoids in pain management in urological chronic pelvic pain syndrome: Gabapentin or pregabalin? Neurourol Urodyn. 2017;36(8):2028-2033. doi:10.1002/nau.23225

498 Cavalcante AN, Sprung J, Schroeder DR, Weingarten TN. Multimodal Analgesic Therapy With Gabapentin and Its Association With Postoperative Respiratory Depression. doi:info:doi/10.1213/ANE.0000000000001719

499 Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study. PLoS Med. 2017;14(10). doi:10.1371/journal.pmed.1002396

500 Deljou A, Hedrick SJ, Portner ER, et al. Pattern of perioperative gabapentinoid use and risk for postoperative naloxone administration. Br J Anaesth. 2018;120(4):798-806. doi:10.1016/j.bja.2017.11.113

501 Federal Drug Administration. FDA In Brief: FDA requires new warnings for gabapentinoids about risk of respiratory depression. Published December 19, 2019. Accessed February 29, 2020. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-requires-new-warnings-gabapentinoids-about-risk-respiratory-depression

502 Doleman B, Heinink TP, Read DJ, Faleiro RJ, Lund JN, Williams JP. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. Anaesthesia. 2015;70(10):1186-1204. doi:10.1111/anae.13179

503 Li X-D, Han C, Yu W-L. Is gabapentin effective and safe in open hysterectomy? A PRISMA compliant meta-analysis of randomized controlled trials. J Clin Anesth. 2017;41:76-83. doi:10.1016/j.jclinane.2017.07.002

504 Alayed N, Alghanaim N, Tan X, Tulandi T. Preemptive use of gabapentin in abdominal hysterectomy: a systematic review and meta-analysis. Obstet Gynecol. 2014;123(6):1221-1229. doi:10.1097/AOG.0000000000000289

505 Sen H, Sizlan A, Yanarates O, et al. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. Anesth Analg. 2009;109(5):1645-1650. doi:10.1213/ANE.0b013e3181b65ea0

506 Asgari Z, Rouholamin S, Nataj M, Sepidarkish M, Hosseini R, Razavi M. Dose ranging effects of pregabalin on pain in patients undergoing laparoscopic hysterectomy: A randomized, double blinded, placebo controlled, clinical trial. J Clin Anesth. 2017;38:13-17. doi:10.1016/j.jclinane.2017.01.015

507 Felder L, Saccone G, Scuotto S, et al. Perioperative gabapentin and post cesarean pain control: A systematic review and meta-analysis of randomized controlled trials. Eur J Obstet Gynecol Reprod Biol. 2019;233:98-106. doi:10.1016/j.ejogrb.2018.11.026

508 Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg. 2007;104(6):1545-1556, table of contents. doi:10.1213/01.ane.0000261517.27532.80

References continued

509 Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med. 2006;31(3):237-247. doi:10.1016/j.rapm.2006.01.005

510 Eipe N, Penning J, Yazdi F, et al. Perioperative use of pregabalin for acute pain—a systematic review and meta-analysis. PAIN. 2015;156(7):1284–1300. doi:10.1097/j.pain.0000000000000173

511 Engelman E, Cateloy F. Efficacy and safety of perioperative pregabalin for post-operative pain: a meta-analysis of randomized-controlled trials. Acta Anaesthesiol Scand. 2011;55(8):927-943. doi:10.1111/j.1399-6576.2011.02471.x

512 El Kenany S, El Tahan MR. Effect of preoperative pregabalin on post-caesarean delivery analgesia: a dose-response study. Int J Obstet Anesth. 2016;26:24-31. doi:10.1016/j.ijoa.2015.11.001

513 Wang Y-M, Xia M, Shan N, et al. Pregabalin can decrease acute pain and postoperative nausea and vomiting in hysterectomy: A meta-analysis. Medicine (Baltimore). 2017;96(31):e7714. doi:10.1097/MD.0000000000007714

514 Cardoso MMS, Leite AO, Santos EA, Gozzani JL, Mathias LAST. Effect of dexamethasone on prevention of postoperative nausea, vomiting and pain after caesarean section: a randomised, placebo-controlled, double-blind trial. Eur J Anaesthesiol EJA. 2013;30(3):102–105. doi:10.1097/EJA.0b013e328356676b

515 Jokela RM, Ahonen JV, Tallgren MK, Marjakangas PC, Korttila KT. The effective analgesic dose of dexamethasone after laparoscopic hysterectomy. Anesth Analg. 2009;109(2):607-615. doi:10.1213/ane.0b013e3181ac0f5c

516 Oliveira GSD, Almeida MD, Benzon HT, McCarthy RJ. Perioperative Single Dose Systemic Dexamethasone for Postoperative PainA Meta-analysis of Randomized Controlled Trials. Anesthesiol J Am Soc Anesthesiol. 2011;115(3):575-588. doi:10.1097/ALN.0b013e31822a24c2

517 Hval K, Kjetil H, Thagaard KS, et al. The prolonged postoperative analgesic effect when dexamethasone is added to a nonsteroidal antiinflammatory drug (rofecoxib) before breast surgery. Anesth Analg. 2007;105(2):481-486. doi:10.1213/01.ane.0000267261.61444.69

518 Kardash KJ, Sarrazin F, Tessler MJ, Velly AM. Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. Anesth Analg. 2008;106(4):1253-1257, table of contents. doi:10.1213/ANE.0b013e318164f319

519 Gupta A, Gupta A, Yadav N. Effect of dexamethasone as an adjuvant to ropivacaine on duration and quality of analgesia in ultrasound-guided transversus abdominis plane block in patients undergoing lower segment cesarean section - A prospective, randomised, single-blinded study. Indian J Anaesth. 2019;63(6):469-474. doi:10.4103/ija.IJA_773_18

520 Deshpande JP, Ghodki PS, Sardesai SP. The Analgesic Efficacy of Dexamethasone Added to Ropivacaine in Transversus Abdominis Plane Block for Transabdominal Hysterectomy under Subarachnoid Block. Anesth Essays Res. 2017;11(2):499-502. doi:10.4103/aer.AER_22_17

521 Maged AM, Deeb WS, Elbaradie S, et al. Comparison of local and intra venous dexamethasone on post operative pain and recovery after caeseream section. A randomized controlled trial. Taiwan J Obstet Gynecol. 2018;57(3):346-350. doi:10.1016/j.tjog.2018.04.004

522 Lirk P, Thiry J, Bonnet M-P, Joshi GP, Bonnet F, PROSPECT Working Group. Pain management after laparoscopic hysterectomy: systematic review of literature and PROSPECT recommendations. Reg Anesth Pain Med. 2019;44(4):425-436. doi:10.1136/rapm-2018-100024

523 Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2008;90(5):1583-1588. doi:10.1016/j.fertnstert.2007.08.051

524 Rafique S, DeCherney AH. MEDICAL MANAGEMENT OF ENDOMETRIOSIS. Clin Obstet Gynecol. 2017;60(3):485-496. doi:10.1097/GRF.0000000000000292

525 Zorbas KA, Economopoulos KP, Vlahos NF. Continuous versus cyclic oral contraceptives for the treatment of endometriosis: a systematic review. Arch Gynecol Obstet. 2015;292(1):37-43. doi:10.1007/s00404-015-3641-1

526 Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ. 2011;343:d6423. doi:10.1136/bmj.d6423

527 Prentice A, Deary AJ, Goldbeck-Wood S, Farquhar C, Smith SK. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst Rev. 2000;(2):CD000346. doi:10.1002/14651858.CD000346

528 Küpker W, Felberbaum RE, Krapp M, Schill T, Malik E, Diedrich K. Use of GnRH antagonists in the treatment of endometriosis. Reprod Biomed Online. 2002;5(1):12-16. doi:10.1016/s1472-6483(10)61590-8

529 Leite FMG, Atallah AN, El Dib R, et al. Cyclobenzaprine for the treatment of myofascial pain in adults. Cochrane Database Syst Rev. 2009;(3):CD006830. doi:10.1002/14651858.CD006830.pub3

530 Henderson DJ, Withington BS, Wilson JA, Morrison LMM. Perioperative Dextromethorphan Reduces Postoperative Pain After Hysterectomy. Anesth Analg. 1999;89(2):399–402. doi:10.1213/00000539-199908000-00028

531 Gwacham NI, Goral J, Miller R, Pitera R, Cinicolo L. Use of Multi-modal Analgesia in Enhanced Recovery After Surgery (ERAS) for Cesarean Sections to Reduce the Use of Opioids [OP02-1B]. Obstet Gynecol. 2020;135:2S. doi:10.1097/01.AOG.0000662880.08512.6b

532 Brinck EC, Tiippana E, Heesen M, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018;12:CD012033. doi:10.1002/14651858.CD012033.pub4

References continued

533 Radvansky BM, Shah K, Parikh A, Sifonios AN, Le V, Eloy JD. Role of Ketamine in Acute Postoperative Pain Management: A Narrative Review. BioMed Research International. doi:https://doi.org/10.1155/2015/749837

534 Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010;113(3):639-646. doi:10.1097/ALN.0b013e3181e90914

535 McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. Acta Anaesthesiol Scand. 2014;58(10):1199-1213. doi:10.1111/aas.12377

536 Patel JC, Patel PB, Acharya H, Nakum K, Tripathi CB. Efficacy and safety of lornoxicam vs ibuprofen in primary dysmenorrhea: a randomized, double-blind, double dummy, active-controlled, cross over study. Eur J Obstet Gynecol Reprod Biol. 2015;188:118-123. doi:10.1016/j.ejogrb.2015.03.005

537 Daniels SE, Paredes-Diaz A, An R, Centofanti R, Tajaddini A. Significant, long-lasting pain relief in primary dysmenorrhea with low-dose naproxen sodium compared with acetaminophen: a double-blind, randomized, single-dose, crossover study. Curr Med Res Opin. 2019;35(12):2139-2147. doi:10.1080/03007995.2019.1654987

538 Mehlisch DR, Ardia A, Pallotta T. Analgesia with ibuprofen arginate versus conventional ibuprofen for patients with dysmenorrhea: a crossover trial. Curr Ther Res Clin Exp. 2003;64(6):327-337. doi:10.1016/S0011-393X(03)00104-8

539 McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for the Reduction of Morphine-Related Side Effects after Major Surgery: A Systematic Review. NIHR Journals Library; 2010. Accessed February 15, 2020. http://www.ncbi.nlm.nih.gov/books/NBK56886/

540 Elia N, Lysakowski C. Does Multimodal Analgesia with Acetaminophen, Nonsteroidal Antiinflammatory Drugs, or Selective Cyclooxygenase-2 Inhibitors and Patient-controlled Analgesia Morphine Offer Advantages over Morphine Alone? Meta-analyses of Randomized Trials. Anesthesiol J Am Soc Anesthesiol. 2005;103(6):1296-1304. doi:0000542-200512000-00025

541 Uribe AA, Arbona FL, Flanigan DC, Kaeding CC, Palettas M, Bergese SD. Comparing the Efficacy of IV Ibuprofen and Ketorolac in the Management of Postoperative Pain Following Arthroscopic Knee Surgery. A Randomized Double-Blind Active Comparator Pilot Study. Front Surg. 2018;5. doi:10.3389/fsurg.2018.00059

542 Abbas MS, Askar OA, Abdel Aleem AA. Pre-emptive ketorolac for prevention of intraoperative shoulder pain in patients undergoing cesarean section: A double blind randomized clinical trial. Asian J Anesthesiol. 2017;55(3):68-72. doi:10.1016/j.aja.2017.07.002

543 Khezri MB, Mosallaei MA-S, Ebtehaj M, Mohammadi N. Comparison of preemptive effect of intravenous ketorolac versus meperidine on postoperative shivering and pain in patients undergoing cesarean section under spinal anesthesia: A prospective, randomized, double-blind study. Casp J Intern Med. 2018;9(2):151-157. doi:10.22088/cjim.9.2.151

544 Blanton E, Lamvu G, Patanwala I, et al. Non-opioid pain management in benign minimally invasive hysterectomy: A systematic review. Am J Obstet Gynecol. 2017;216(6):557-567. doi:10.1016/j.ajog.2016.12.175

545 Ulm MA, ElNaggar AC, Tillmanns TD. Celecoxib versus ketorolac following robotic hysterectomy for the management of postoperative pain: An open-label randomized control trial. Gynecol Oncol. 2018;151(1):124-128. doi:10.1016/j.ygyno.2018.08.015

546 Bell S, Rennie T, Marwick CA, Davey P. Effects of peri-operative nonsteroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function. Cochrane Database Syst Rev. 2018;2018(11). doi:10.1002/14651858.CD011274.pub2

547 Teerawattananon C, Tantayakom P, Suwanawiboon B, Katchamart W. Risk of perioperative bleeding related to highly selective cyclooxygenase-2 inhibitors: A systematic review and meta-analysis. Semin Arthritis Rheum. 2017;46(4):520-528. doi:10.1016/j.semarthrit.2016.07.008

548 Gobble RM, Hoang HLT, Kachniarz B, Orgill DP. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. Plast Reconstr Surg. 2014;133(3):741-755. doi:10.1097/01.prs.0000438459.60474.b5

549 Richardson MD, Palmeri NO, Williams SA, et al. Routine perioperative ketorolac administration is not associated with hemorrhage in pediatric neurosurgery patients. J Neurosurg Pediatr. 2016;17(1):107-115. doi:10.3171/2015.4.PEDS14411

550 Stephens DM, Richards BG, Schleicher WF, Zins JE, Langstein HN. Is ketorolac safe to use in plastic surgery? A critical review. Aesthet Surg J. 2015;35(4):462-466. doi:10.1093/asj/sjv005

551 Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. JAMA. 1996;275(5):376-382.

552 Access Data FDA Toradol - Ketorolac Tromethamine. Accessed July 17, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019645s019lbl.pdf

553 Lanas A, García-Rodríguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut. 2006;55(12):1731-1738. doi:10.1136/gut.2005.080754

554 Lanza FL, Chan FKL, Quigley EMM, Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104(3):728-738. doi:10.1038/ajg.2009.115

555 Boardman LA, Cooper AS, Blais LR, Raker CA. Topical gabapentin in the treatment of localized and generalized vulvodynia. Obstet Gynecol. 2008;112(3):579-585. doi:10.1097/AOG.0b013e3181827c77

References continued

556 Nyirjesy P, Lev-Sagie A, Mathew L, Culhane J. Topical Amitriptyline-Baclofen Cream for the Treatment of Provoked Vestibulodynia. J Low Genit Tract Dis. 2009;13(4):230-236. doi:10.1097/LGT.0b013e31819663ee

557 Zolnoun DA, Hartmann KE, Steege JF. Overnight 5% lidocaine ointment for treatment of vulvar vestibulitis. Obstet Gynecol. 2003;102(1):84-87. doi:10.1016/s0029-7844(03)00368-5

558 Astin JA. Mind–Body Therapies for the Management of Pain. Clin J Pain. 2004;20(1):27–32.

559 Nicholls JL, Azam MA, Burns LC, et al. Psychological treatments for the management of postsurgical pain: a systematic review of randomized controlled trials. Patient Relat Outcome Meas. 2018;9:49-64. doi:10.2147/PROM.S121251

560 Vranceanu A-M, Hageman M, Strooker J, ter Meulen D, Vrahas M, Ring D. A preliminary RCT of a mind body skills based intervention addressing mood and coping strategies in patients with acute orthopaedic trauma. Injury. 2015;46(4):552-557. doi:10.1016/j.injury.2014.11.001

561 Topcu SY, Findik UY. Effect of Relaxation Exercises on Controlling Postoperative Pain. Pain Manag Nurs. 2012;13(1):11-17. doi:10.1016/j.pmn.2010.07.006

562 Zhang MWB, Ho RCM, Cassin SE, Hawa R, Sockalingam S. Online and smartphone based cognitive behavioral therapy for bariatric surgery patients: Initial pilot study. Technol Health Care. 2015;23(6):737-744. doi:10.3233/THC-151026

563 Bradt J, Dileo C, Potvin N. Music for stress and anxiety reduction in coronary heart disease patients. Cochrane Database Syst Rev. 2013;(12). doi:10.1002/14651858.CD006577.pub3

564 Lakhan SE, Sheafer H, Tepper D. The Effectiveness of Aromatherapy in Reducing Pain: A Systematic Review and Meta-Analysis. Pain Research and Treatment. doi:https://doi.org/10.1155/2016/8158693

565 Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17(2):131-157. doi:10.1016/j.jpain.2015.12.008

566 Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The Changing Face of Heroin Use in the United States: A Retrospective Analysis of the Past 50 Years. JAMA Psychiatry. 2014;71(7):821-826. doi:10.1001/jamapsychiatry.2014.366

567 Mathers BM, Degenhardt L, Phillips B, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. Lancet Lond Engl. 2008;372(9651):1733-1745. doi:10.1016/S0140-6736(08)61311-2

568 United Nations Office on Drugs and Crime. Women who inject drugs and HIV: Addressing specific needs. Published 2016. Accessed June 27, 2020. http://www.unodc.org/documents/hiv-aids/publications/WOMEN_POLICY_BRIEF2014.pdf

569 Iversen J, Page K, Madden A, Maher L. HIV, HCV, and Health-Related Harms Among Women Who Inject Drugs: Implications for Prevention and Treatment. J Acquir Immune Defic Syndr 1999. 2015;69 Suppl 2:S176-181. doi:10.1097/QAI.0000000000000659

570 El-Basse N, Gilbert L, Wu E, Go H, Hill J. HIV and intimate partner violence among methadone-maintained women in New York City. Soc Sci Med. 2005;61(1):171-183. doi:10.1016/j.socscimed.2004.11.035

571 Shannon K, Csete J. Violence, condom negotiation, and HIV/STI risk among sex workers. JAMA. 2010;304(5):573-574. doi:10.1001/jama.2010.1090

572 Tracy D, Hahn JA, Fuller Lewis C, et al. Higher risk of incident hepatitis C virus among young women who inject drugs compared with young men in association with sexual relationships: a prospective analysis from the UFO Study cohort. BMJ Open. 2014;4(5):e004988. doi:10.1136/bmjopen-2014-004988

573 Miller CL, Wood E, Spittal PM, et al. The future face of coinfection: prevalence and incidence of HIV and hepatitis C virus coinfection among young injection drug users. J Acquir Immune Defic Syndr 1999. 2004;36(2):743-749. doi:10.1097/00126334-200406010-00012

574 Iversen J, Wand H, Gonnermann A, Maher L, collaboration of Australian Needle and Syringe Programs. Gender differences in hepatitis C antibody prevalence and risk behaviours amongst people who inject drugs in Australia 1998-2008. Int J Drug Policy. 2010;21(6):471-476. doi:10.1016/j.drugpo.2010.04.004

575 Substance Abuse and Mental Health Services Administration. Medication and Counseling Treatment. Published 2020. https://www.samhsa.gov/medication-assisted-treatment/treatment

576 Principles of Effective Treatment: A Research-Based Guide (Third Edition). National Institute on Drug Abuse. Published January 2018. Accessed July 30, 2020. https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/principles-effective-treatment

577 National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Global Health; Board on Health Sciences Policy; Global Forum on Innovation in Health Professional Education; Forum on Neuroscience and Nervous System Disorders. The Role of Nonpharmacological Approaches to Pain Management: Proceedings of a Workshop. (Stroud C, Posey Norris SM, Bain L, eds.). National Academies Press (US); 2019. Accessed July 30, 2020. http://www.ncbi.nlm.nih.gov/books/NBK541702/

578 Wheeler E, Jones TS, Gilbert MK, Davidson PJ, Centers for Disease Control and Prevention (CDC). Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014. MMWR Morb Mortal Wkly Rep. 2015;64(23):631-635.

579 McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addict Abingdon Engl. 2016;111(7):1177-1187. doi:10.1111/add.13326

References continued

580 Mueller SR, Walley AY, Calcaterra SL, Glanz JM, Binswanger IA. A Review of Opioid Overdose Prevention and Naloxone Prescribing: Implications for Translating Community Programming Into Clinical Practice. Subst Abuse. 2015;36(2):240-253. doi:10.1080/08897077.2015.1010032

581 Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ. 2013;346:f174. doi:10.1136/bmj.f174

582 Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. Ann Intern Med. 2013;158(1):1-9. doi:10.7326/0003-4819-158-1-201301010-00003

583 Sherman S, Nyeong Park J, Glick J, Christensen T, Morales K. Fentanyl Overdose Reduction Checking Analysis Study (FORECAST). Johns Hopkins Bloomberg School of Public Health. Published February 6, 2018. Accessed July 30, 2020. https://americanhealth.jhu.edu/sites/default/files/inline-files/Fentanyl_Executive_Summary_032018.pdf

584 Goldman JE, Waye KM, Periera KA, Krieger MS, Yedinak JL, Marshall BDL. Perspectives on rapid fentanyl test strips as a harm reduction practice among young adults who use drugs: a qualitative study. Harm Reduct J. 2019;16(1):1-11. doi:10.1186/s12954-018-0276-0

585 Lambdin BH, Zibbell J, Wheeler E, Kral AH. Identifying gaps in the implementation of naloxone programs for laypersons in the United States. Int J Drug Policy. 2017;52:52-55. doi:10.1016/j.drugpo.2017.11.017

586 Abuse NI on D. Kratom DrugFacts. National Institute on Drug Abuse. Published April 8, 2019. Accessed July 30, 2020. https://www.drugabuse.gov/publications/drugfacts/kratom

587 PrEP | HIV Basics | HIV/AIDS | CDC. Published June 4, 2020. Accessed July 30, 2020. https://www.cdc.gov/hiv/basics/prep.html

588 Palmateer N, Kimber J, Hickman M, Hutchinson S, Rhodes T, Goldberg D. Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews. Addiction. 2010;105(5):844-859. doi:10.1111/j.1360-0443.2009.02888.x

589 Wodak A, Cooney A. Effectiveness of Sterile Needle and Syringe Programming in Reducing HIV/AIDS Among Injecting Drug Users. World Health Organization. Published 2004. Accessed September 12, 2019. https://apps.who.int/iris/bitstream/handle/10665/43107/9241591641.pdf

590 Yoast R, Williams MA, Deitchman SD, Champion HC. Report of the Council on Scientific Affairs: methadone maintenance and needle-exchange programs to reduce the medical and public health consequences of drug abuse. J Addict Dis. 2001;20(2):15-40. doi:10.1300/J069v20n02_03

591 2018 National Survey on Drug Use and Health: Women. Substance Abuse and Mental Health Services Administration U.S. Department of Health and Human Services. Published 2018. Accessed June 22, 2020. https://www.samhsa.gov/data/sites/default/files/reports/rpt23250/5_Women_2020_01_14_508.pdf

592 Strathdee SA, Latka M, Campbell J, et al. Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. Clin Infect Dis Off Publ Infect Dis Soc Am. 2005;40 Suppl 5:S304-312. doi:10.1086/427445

593 Frajzyngier V, Neaigus A, Gyarmathy VA, Miller M, Friedman SR. Gender differences in injection risk behaviors at the first injection episode. Drug Alcohol Depend. 2007;89(2-3):145-152. doi:10.1016/j.drugalcdep.2006.12.021

594 Lazuardi E, Worth H, Saktiawati AMI, Spooner C, Padmawati R, Subronto Y. Boyfriends and injecting: the role of intimate male partners in the life of women who inject drugs in Central Java. Cult Health Sex. 2012;14(5):491-503. doi:10.1080/13691058.2012.671960

595 Barnard MA. Needle sharing in context: patterns of sharing among men and women injectors and HIV risks. Addict Abingdon Engl. 1993;88(6):805-812. doi:10.1111/j.1360-0443.1993.tb02094.x

596 Bourgois P, Prince B, Moss A. The Everyday Violence of Hepatitis C Among Young Women Who Inject Drugs in San Francisco. Hum Organ. 2004;63(3):253-264. doi:10.17730/humo.63.3.h1phxbhrb7m4mlv0

597 El-Bassel N, Gilbert L, Witte S, Wu E, Hunt T, Remien RH. Couple-based HIV prevention in the United States: advantages, gaps, and future directions. J Acquir Immune Defic Syndr 1999. 2010;55 Suppl 2:S98-101. doi:10.1097/QAI.0b013e3181fbf407

598 Morris MD, Evans J, Montgomery M, et al. Intimate injection partnerships are at elevated risk of high-risk injecting: a multi-level longitudinal study of HCV-serodiscordant injection partnerships in San Francisco, CA. PloS One. 2014;9(10):e109282. doi:10.1371/journal.pone.0109282

599 Hope V, Kimber J, Vickerman P, Hickman M, Ncube F. Frequency, factors and costs associated with injection site infections: findings from a national multi-site survey of injecting drug users in England. BMC Infect Dis. 2008;8:120. doi:10.1186/1471-2334-8-120

600 Topp L, Iversen J, Conroy A, Salmon AM, Maher L, Collaboration of Australian NSPs. Prevalence and predictors of injecting-related injury and disease among clients of Australia's needle and syringe programs. Aust N Z J Public Health. 2008;32(1):34-37. doi:10.1111/j.1753-6405.2008.00163.x

601 Spijkerman IJ, van Ameijden EJ, Mientjes GH, Coutinho RA, van den Hoek A. Human immunodeficiency virus infection and other risk factors for skin abscesses and endocarditis among injection drug users. J Clin Epidemiol. 1996;49(10):1149-1154. doi:10.1016/0895-4356(96)00180-1

602 Medicine I of. Clinical Preventive Services for Women: Closing the Gaps.; 2011. doi:10.17226/13181

References continued

603 Department of Health and Human Services. Costs of Intimate Partner Violence Against Women in the United States. Centers for Disease Control and Prevention. Published March 2003. Accessed July 30, 2020. https://www.cdc.gov/violenceprevention/pdf/IPVbook-a.pdf

604 Centers for Disease Control and Prevention. The National Intimate Partner and Sexual Violence Survey (NISVS) |Violence Prevention|Injury Center|CDC. Accessed July 30, 2020. https://www.cdc.gov/violenceprevention/datasources/nisvs/index.html

605 Coker AL. Does physical intimate partner violence affect sexual health? A systematic review. Trauma Violence Abuse. 2007;8(2):149-177. doi:10.1177/1524838007301162

606 Li Y, Marshall CM, Rees HC, Nunez A, Ezeanolue EE, Ehiri JE. Intimate partner violence and HIV infection among women: a systematic review and meta-analysis. J Int AIDS Soc. 2014;17:18845. doi:10.7448/IAS.17.1.18845

607 Illangasekare S, Tello M, Hutton H, et al. Clinical and mental health correlates and risk factors for intimate partner violence among HIV-positive women in an inner-city HIV clinic. Womens Health Issues Off Publ Jacobs Inst Womens Health. 2012;22(6):e563-569. doi:10.1016/j.whi.2012.07.007

608 ACOG Committee Opinion No. 518: Intimate partner violence. Obstet Gynecol. 2012;119(2 Pt 1):412-417. doi:10.1097/AOG.0b013e318249ff74

609 El-Bassel N, Wechsberg WM, Shaw SA. Dual HIV risk and vulnerabilities among women who use or inject drugs: no single prevention strategy is the answer. Curr Opin HIV AIDS. 2012;7(4):326-331. doi:10.1097/COH.0b013e3283536ab2

610 Azim T, Bontell I, Strathdee SA. Women, drugs and HIV. Int J Drug Policy. 2015;26 Suppl 1:S16-21. doi:10.1016/j.drugpo.2014.09.003

611 Morris MD, Lemus H, Wagner KD, et al. Factors associated with pathways toward concurrent sex work and injection drug use among female sex workers who inject drugs in northern Mexico. Addict Abingdon Engl. 2013;108(1):161-170. doi:10.1111/j.1360-0443.2012.04016.x

612 Maher L. Hidden in the Light: Occupational Norms among Crack-Using Street-Level Sex Workers: J Drug Issues. Published online January 1, 1996. doi:10.1177/002204269602600109

613 Pinkham S, Malinowska-Sempruch K. Women, harm reduction and HIV. Reprod Health Matters. 2008;16(31):168-181. doi:10.1016/S0968-8080(08)31345-7

614 Weber AE, Tyndall MW, Spittal PM, et al. High pregnancy rates and reproductive health indicators among female injection-drug users in Vancouver, Canada. Eur J Contracept Reprod Health Care Off J Eur Soc Contracept. 2003;8(1):52-58.

615 Duff P, Shoveller J, Zhang R, Alexson D, Montaner JSG, Shannon K. High lifetime pregnancy and low contraceptive usage among sex workers who use drugs- an unmet reproductive health need. BMC Pregnancy Childbirth. 2011;11:61. doi:10.1186/1471-2393-11-61

616 Wilder C, Lewis D, Winhusen T. Medication assisted treatment discontinuation in pregnant and postpartum women with opioid use disorder. Drug Alcohol Depend. 2015;149:225-231. doi:10.1016/j.drugalcdep.2015.02.012

617 Mack KA, Centers for Disease Control and Prevention (CDC). Drug-induced deaths - United States, 1999-2010. MMWR Suppl. 2013;62(3):161-163.

618 Jones CM, Logan J, Gladden RM, Bohm MK. Vital Signs: Demographic and Substance Use Trends Among Heroin Users - United States, 2002-2013. MMWR Morb Mortal Wkly Rep. 2015;64(26):719-725.

619 Opioid Overdose Deaths by Gender. Kaiser. Published February 13, 2020. Accessed July 30, 2020. https://www.kff.org/other/state-indicator/opioid-overdose-deaths-by-gender/

620 Back SE, Payne RL, Wahlquist AH, et al. Comparative Profiles of Men and Women with Opioid Dependence: Results from a National Multisite Effectiveness Trial. Am J Drug Alcohol Abuse. 2011;37(5):313-323. doi:10.3109/00952990.2011.596982

621 Hernandez-Avila CA, Rounsaville BJ, Kranzler HR. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. Drug Alcohol Depend. 2004;74(3):265-272. doi:10.1016/j.drugalcdep.2004.02.001

622 Hitschfeld MJ, Schneekloth TD, Ebbert JO, et al. Female smokers have the highest alcohol craving in a residential alcoholism treatment cohort. Drug Alcohol Depend. 2015;150:179-182. doi:10.1016/j.drugalcdep.2015.02.016

623 Kennedy AP, Epstein DH, Phillips KA, Preston KL. Sex differences in cocaine/heroin users: Drug-use triggers and craving in daily life. Drug Alcohol Depend. 2013;132(1):29-37. doi:10.1016/j.drugalcdep.2012.12.025

624 Shiffman S, Rathbun SL. Point process analyses of variations in smoking rate by setting, mood, gender, and dependence. Psychol Addict Behav. 2011;25(3):501-510. doi:10.1037/a0022178

625 Back SE, Lawson KM, Singleton LM, Brady KT. Characteristics and correlates of men and women with prescription opioid dependence. Addict Behav. 2011;36(8):829-834. doi:10.1016/j.addbeh.2011.03.013

626 Mills KL, Teesson M, Ross J, Darke S, Shanahan M. The costs and outcomes of treatment for opioid dependence associated with posttraumatic stress disorder. Psychiatr Serv Wash DC. 2005;56(8):940-945. doi:10.1176/appi.ps.56.8.940

627 U.S. Department of Health and Human Services. 2013 Trans-HHS Intimate Partner Violence Screening and Counseling: Research Symposium. Published October 5, 2015. https://sis.nlm.nih.gov/outreach/2013IPVsymposium.html

628 Cavanaugh CE, Petras H, Martins SS. Gender-specific profiles of adverse childhood experiences, past year mental and substance use disorders, and their associations among a national sample of adults in the United States. Soc Psychiatry Psychiatr Epidemiol. 2015;50(8):1257-1266. doi:10.1007/s00127-015-1024-3

References continued

629 Watamura S, Brown S. Parental History of Adversity and Child Well-Being: INsight from Colorado. Colorado Office of Early Childhood Department of Human Services. Accessed July 30, 2020. https://eccp.civiccanopy.org/wp-content/uploads/2016/08/OEC_2017_ACEs_Report.pdf

630 Najavits LM, Weiss RD, Shaw SR. The Link Between Substance Abuse and Posttraumatic Stress Disorder in Women. Am J Addict. 1997;6(4):273-283. doi:10.1111/j.1521-0391.1997.tb00408.x

631 NCSACW - Trauma-Informed Care. Accessed June 11, 2020. https://ncsacw.samhsa.gov/topics/trauma-informed-care.aspx

632 Quinn K, Boone L, Scheidell JD, et al. The relationships of childhood trauma and adulthood prescription pain reliever misuse and injection drug use. Drug Alcohol Depend. 2016;169:190-198. doi:10.1016/j.drugalcdep.2016.09.021

633 Felitti VJ. [Origins of addictive behavior: evidence from a study of stressful chilhood experiences]. Prax Kinderpsychol Kinderpsychiatr. 2003;52(8):547-559.

634 Finestone HM, Stenn P, Davies F, Stalker C, Fry R, Koumanis J. Chronic pain and health care utilization in women with a history of childhood sexual abuse11Submitted for publication November 10, 1997; final revision received July 15, 1999; accepted July 21, 1999. Child Abuse Negl. 2000;24(4):547-556. doi:10.1016/S0145-2134(00)00112-5

635 Davis DA, Luecken LJ, Zautra AJ. Are reports of childhood abuse related to the experience of chronic pain in adulthood? A meta-analytic review of the literature. Clin J Pain. 2005;21(5):398-405. doi:10.1097/01.ajp.0000149795.08746.31

636 Sachs-Ericsson N, Kendall-Tackett K, Hernandez A. Childhood abuse, chronic pain, and depression in the National Comorbidity Survey. Child Abuse Negl. 2007;31(5):531-547. doi:10.1016/j.chiabu.2006.12.007

637 Anda RF, Brown DW, Felitti VJ, Dube SR, Giles WH. Adverse childhood experiences and prescription drug use in a cohort study of adult HMO patients. BMC Public Health. 2008;8:198. doi:10.1186/1471-2458-8-198

638 Leeb RT, Lewis T, Zolotor AJ. A Review of Physical and Mental Health Consequences of Child Abuse and Neglect and Implications for Practice. Am J Lifestyle Med. 2011;5(5):454-468. doi:10.1177/1559827611410266

639 Hillis SD, Anda RF, Felitti VJ, Nordenberg D, Marchbanks PA. Adverse childhood experiences and sexually transmitted diseases in men and women: a retrospective study. Pediatrics. 2000;106(1):E11. doi:10.1542/peds.106.1.e11

640 Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, Anda RF. Adverse childhood experiences and the risk of depressive disorders in adulthood. J Affect Disord. 2004;82(2):217-225. doi:10.1016/j.jad.2003.12.013

641 Gilbert LK, Breiding MJ, Merrick MT, et al. Childhood adversity and adult chronic disease: an update from ten states and the District of Columbia, 2010. Am J Prev Med. 2015;48(3):345-349. doi:10.1016/j.amepre.2014.09.006

642 Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. JAMA. 2001;286(24):3089-3096. doi:10.1001/jama.286.24.3089

643 Tuchman E. Women and addiction: the importance of gender issues in substance abuse research. J Addict Dis. 2010;29(2):127-138. doi:10.1080/10550881003684582

644 Rowan-Szal GA, Chatham LR, Joe GW, Simpson DD. Services provided during methadone treatment. A gender comparison. J Subst Abuse Treat. 2000;19(1):7-14. doi:10.1016/s0740-5472(99)00091-4

645 Maeda A, Bateman BT, Clancy CR, Creanga AA, Leffert LR. Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes. Anesthesiology. 2014;121(6):1158-1165. doi:10.1097/ALN.0000000000000472

646 Shen Y, Lo-Ciganic W-H, Segal R, Goodin AJ. Prevalence of substance use disorder and psychiatric comorbidity burden among pregnant women with opioid use disorder in a large administrative database, 2009–2014. J Psychosom Obstet Gynecol. 2020;0(0):1-7. doi:10.1080/0167482X.2020.1727882

647 Binder T, Vavrinková B. Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department. Neuro Endocrinol Lett. 2008;29(1):80-86.

648 Committee Opinion No. 711 Summary: Opioid Use and Opioid Use Disorder in Pregnancy. Obstet Gynecol. 2017;130(2):488–489. doi:10.1097/AOG.0000000000002229

649 Ordean A, Wong S, Graves L. No. 349-Substance Use in Pregnancy. J Obstet Gynaecol Can JOGC J Obstet Gynecol Can JOGC. 2017;39(10):922-937.e2. doi:10.1016/j.jogc.2017.04.028

650 Zedler BK, Mann AL, Kim MM, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. Addict Abingdon Engl. 2016;111(12):2115-2128. doi:10.1111/add.13462

651 Clinical Guidance for Treating Pregnant and Parenting Women With Opioid Use Disorder and Their Infants | Publications and Digital Products. Substance Abuse and Mental Health Services Administration. Published 2018. Accessed June 22, 2020. https://store.samhsa.gov/product/Clinical-Guidance-for-Treating-Pregnant-and-Parenting-Women-With-Opioid-Use-Disorder-and-Their-Infants/SMA18-5054

652 Substance Use During Pregnancy. Guttmacher Institute. Published March 14, 2016. Accessed July 30, 2020. https://www.guttmacher.org/state-policy/explore/substance-use-during-pregnancy

653 Howard H. Experiences of opioid-dependent women in their prenatal and postpartum care: Implications for social workers in health care. Soc Work Health Care. 2016;55(1):61-85. doi:10.1080/00981389.2015.1078427

654 Arnaudo CL, Andraka-Christou B, Allgood K. Psychiatric Co-Morbidities in Pregnant Women with Opioid Use Disorders: Prevalence, Impact, and Implications for Treatment. Curr Addict Rep. 2017;4(1):1-13. doi:10.1007/s40429-017-0132-4

References continued

655 Metz TD, Rovner P, Hoffman MC, Allshouse AA, Beckwith KM, Binswanger IA. Maternal Deaths From Suicide and Overdose in Colorado, 2004–2012. Obstet Gynecol. 2016;128(6):1233-1240. doi:10.1097/AOG.0000000000001695

656 Maternal Mortality in Colorado, 2014-2016. Colorado Department of Public Health & Environment (CDPHE). Published July 2020. Accessed July 27, 2020. https://drive.google.com/file/d/11sB0qnM1DmfCA-Z87el3KMHN6oBy5t2y/view?usp=sharing&usp=embed_facebook

657 Schiff DM, Nielsen T, Terplan M, et al. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. Obstet Gynecol. 2018;132(2):466-474. doi:10.1097/AOG.0000000000002734

658 Wolf ER, Tong ST, Sabo RT, et al. A state-level study of opioid use disorder treatment access and neonatal abstinence syndrome. BMC Pediatr. 2019;19(1):371. doi:10.1186/s12887-019-1718-x

659 Winkelman TNA, Villapiano N, Kozhimannil KB, Davis MM, Patrick SW. Incidence and Costs of Neonatal Abstinence Syndrome Among Infants With Medicaid: 2004–2014. Pediatrics. 2018;141(4). doi:10.1542/peds.2017-3520

660 Jilani SM. Evaluation of State-Mandated Reporting of Neonatal Abstinence Syndrome — Six States, 2013–2017. MMWR Morb Mortal Wkly Rep. 2019;68. doi:10.15585/mmwr.mm6801a2

661 Office USGA. Medicaid: Opioid Use Disorder Services for Pregnant and Postpartum Women, and Children. 2019;(GAO-20-40). Accessed July 30, 2020. https://www.gao.gov/products/GAO-20-40

662 Honein MA, Boyle C, Redfield RR. Public Health Surveillance of Prenatal Opioid Exposure in Mothers and Infants. Pediatrics. 2019;143(3). doi:10.1542/peds.2018-3801

663 Winklbaur B, Baewert A, Jagsch R, et al. Association between Prenatal Tobacco Exposure and Outcome of Neonates Born to Opioid-Maintained Mothers. Eur Addict Res. 2009;15(3):150-156. doi:10.1159/000216466

664 Maremmani I, Pani PP, Mellini A, et al. Alcohol and cocaine use and abuse among opioid addicts engaged in a methadone maintenance treatment program. J Addict Dis. 2007;26(1):61-70. doi:10.1300/J069v26n01_08

665 Nava F, Caldiroli E, Premi S, Lucchini A. Relationship between plasma cortisol levels, withdrawal symptoms and craving in abstinent and treated heroin addicts. J Addict Dis. 2006;25(2):9-16. doi:10.1300/J069v25n02_02

666 Abdel-Latif ME, Pinner J, Clews S, Cooke F, Lui K, Oei J. Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug-dependent mothers. Pediatrics. 2006;117(6):e1163-1169. doi:10.1542/peds.2005-1561

667 Colorado Hospitals Substance Exposed Newborns. Accessed July 30, 2020. https://cpcqc.org/qii/chosen/

668 Guidelines for identification and management of substance use and substance use disorders in pregnancy. Published November 19, 2014. Accessed July 21, 2020. https://www.who.int/publications-detail-redirect/9789241548731

669 Wright TE, Terplan M, Ondersma SJ, et al. The role of screening, brief intervention, and referral to treatment in the perinatal period. Am J Obstet Gynecol. 2016;215(5):539-547. doi:10.1016/j.ajog.2016.06.038

670 American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 422: at-risk drinking and illicit drug use: ethical issues in obstetric and gynecologic practice. Obstet Gynecol. 2008;112(6):1449-1460. doi:10.1097/AOG.0b013e318192499b

671 Chang G, McNamara TK, Orav EJ, et al. Brief intervention for prenatal alcohol use: a randomized trial. Obstet Gynecol. 2005;105(5 Pt 1):991-998. doi:10.1097/01.AOG.0000157109.05453.84

672 Chang G, Wilkins-Haug L, Berman S, Goetz MA. Brief intervention for alcohol use in pregnancy: a randomized trial. Addict Abingdon Engl. 1999;94(10):1499-1508. doi:10.1046/j.1360-0443.1999.941014996.x

673 O'Connor MJ, Whaley SE. Brief intervention for alcohol use by pregnant women. Am J Public Health. 2007;97(2):252-258. doi:10.2105/AJPH.2005.077222

674 Montag AC, Brodine SK, Alcaraz JE, et al. Effect of Depression on Risky Drinking and Response to a Screening, Brief Intervention, and Referral to Treatment Intervention. Am J Public Health. 2015;105(8):1572-1576. doi:10.2105/AJPH.2015.302688

675 Montag AC, Brodine SK, Alcaraz JE, et al. Preventing alcohol-exposed pregnancy among an American Indian/Alaska Native population: effect of a screening, brief intervention, and referral to treatment intervention. Alcohol Clin Exp Res. 2015;39(1):126-135. doi:10.1111/acer.12607

676 Ondersma SJ, Beatty JR, Svikis DS, et al. Computer-Delivered Screening and Brief Intervention for Alcohol Use in Pregnancy: A Pilot Randomized Trial. Alcohol Clin Exp Res. 2015;39(7):1219-1226. doi:10.1111/acer.12747

677 Pollick SA, Beatty JR, Sokol RJ, et al. Acceptability of a computerized brief intervention for alcohol among abstinent but at-risk pregnant women. Subst Abuse. 2015;36(1):13-20. doi:10.1080/08897077.2013.857631

678 Ferreira-Borges C. Effectiveness of a brief counseling and behavioral intervention for smoking cessation in pregnant women. Prev Med. 2005;41(1):295-302. doi:10.1016/j.ypmed.2004.11.013

679 Bailey BA, Sokol RJ. Pregnancy and alcohol use: evidence and recommendations for prenatal care. Clin Obstet Gynecol. 2008;51(2):436-444. doi:10.1097/GRF.0b013e31816fea3d

680 Svikis DS, Reid-Quiñones K. Screening and prevention of alcohol and drug use disorders in women. Obstet Gynecol Clin North Am. 2003;30(3):447-468. doi:10.1016/s0889-8545(03)00082-2

681 Diekman ST, Floyd RL, Découflé P, Schulkin J, Ebrahim SH, Sokol RJ. A survey of obstetrician-gynecologists on their patients' alcohol use during pregnancy. Obstet Gynecol. 2000;95(5):756-763. doi:10.1016/s0029-7844(99)00616-x

682 Oser C, Biebel E, Harris M, Klein E, Leukefeld C. Gender differences in provider's use of a standardized screening tool for prenatal substance use. J Addict Med. 2011;5(1):36-42. doi:10.1097/ADM.0b013e3181ccec2e

References continued

683 ling W, Stephenson D, Vasti E. Guidelines for Physicians Working in California Opioid Treatment Programs. California Department of Health Care Services. Published 2019. Accessed July 30, 2020. https://cdn.ymaws.com/csam-asam.org/resource/collection/0BE82575-F893-4CF6-8954-B2CAF524DCFE/CSAM-guidelines.pdf

684 McCance-Katz, M.D., PhD EF. The National Survey on Drug Use and Health: 2017. Substance Abuse and Mental Health Services Administration. Published 2017. Accessed June 24, 2020. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/nsduh-ppt-09-2018/nsduh-ppt-09-2018.pdf

685 Kim SS, Kaplowitz S, Johnston MV. The effects of physician empathy on patient satisfaction and compliance. Eval Health Prof. 2004;27(3):237-251. doi:10.1177/0163278704267037

686 Mercer SW, Reynolds WJ. Empathy and quality of care. Br J Gen Pract J R Coll Gen Pract. 2002;52 Suppl:S9-12.

687 Stewart MA. Effective physician-patient communication and health outcomes: a review. CMAJ Can Med Assoc J J Assoc Medicale Can. 1995;152(9):1423-1433.

688 Zhu H, Wu L-T. Discharge against medical advice from hospitalizations for substance use disorders: The potential impact of the Affordable Care Act. Drug Alcohol Depend. 2019;197:115-119. doi:10.1016/j.drugalcdep.2018.12.032

689 Jones HE, Deppen K, Hudak ML, et al. Clinical care for opioid-using pregnant and postpartum women: the role of obstetric providers. Am J Obstet Gynecol. 2014;210(4):302-310. doi:10.1016/j.ajog.2013.10.010

690 Roberts SCM, Nuru-Jeter A. Women's perspectives on screening for alcohol and drug use in prenatal care. Womens Health Issues Off Publ Jacobs Inst Womens Health. 2010;20(3):193-200. doi:10.1016/j.whi.2010.02.003

691 Stone R. Pregnant women and substance use: fear, stigma, and barriers to care. Health Justice. 2015;3(1):2. doi:10.1186/s40352-015-0015-5

692 Hoffman J. Most Doctors Are Ill-Equipped to Deal With the Opioid Epidemic. Few Medical Schools Teach Addiction. The New York Times. Published September 10, 2018. https://www.nytimes.com/2018/09/10/health/addiction-medical-schools-treatment.html

693 Brezing C. Opioid Use Disorder: Update on Diagnosis and Treatment. Psychiatric Times. Published April 30, 2015. Accessed February 16, 2020. https://www.psychiatrictimes.com/opioid-use-disorder-update-diagnosis-and-treatment

694 Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine Treatment for Hospitalized, Opioid-Dependent Patients: A Randomized Clinical Trial. JAMA Intern Med. 2014;174(8):1369-1376. doi:10.1001/jamainternmed.2014.2556

695 Carroll KM, Weiss RD. The Role of Behavioral Interventions in Buprenorphine Maintenance Treatment: A Review. Am J Psychiatry. 2017;174(8):738-747. doi:10.1176/appi.ajp.2016.16070792

696 Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. Am J Med. 2013;126(1):74.e11-17. doi:10.1016/j.amjmed.2012.07.005

697 Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Engl J Med. 2006;355(4):365-374. doi:10.1056/NEJMoa055255

698 Ling W, Hillhouse M, Ang A, Jenkins J, Fahey J. Comparison of behavioral treatment conditions in buprenorphine maintenance. Addict Abingdon Engl. 2013;108(10):1788-1798. doi:10.1111/add.12266

699 Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry. 2011;68(12):1238-1246. doi:10.1001/archgenpsychiatry.2011.121

700 Pettinati HM, O'Brien CP, Dundon WD. Current status of co-occurring mood and substance use disorders: a new therapeutic target. Am J Psychiatry. 2013;170(1):23-30. doi:10.1176/appi.ajp.2012.12010112

701 A Collaborative Approach to the Treatment of Pregnant Women with Opioid Use Disorders. Substance Abuse and Mental Health Services Administration. Published 2016. Accessed June 23, 2020. https://ncsacw.samhsa.gov/files/Collaborative_Approach_508.pdf

702 Burns L, Mattick R, Lim K, Wallace C. Methadone in pregnancy: Treatment retention and neonatal outcomes. Addict Abingdon Engl. 2007;102:264-270. doi:10.1111/j.1360-0443.2006.01651.x

703 Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2004;(3):CD002207. doi:10.1002/14651858.CD002207.pub2

704 Jones HE, Heil SH, Baewert A, et al. Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review. Addict Abingdon Engl. 2012;107 Suppl 1:5-27. doi:10.1111/j.1360-0443.2012.04035.x

705 Hulse GK, O'Neil G, Arnold-Reed DE. Methadone maintenance vs. implantable naltrexone treatment in the pregnant heroin user. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2004;85(2):170-171. doi:10.1016/j.ijgo.2003.10.001

706 Chutuape MA, Jasinski DR, Fingerhood MI, Stitzer ML. One-, Three-, and Six-Month Outcomes After Brief Inpatient Opioid Detoxification. Am J Drug Alcohol Abuse. 2001;27(1):19-44. doi:10.1081/ADA-100103117

707 Strain E. Opioid use disorder: Epidemiology, pharmacology, clinical manifestations, course, screening, assessment, and diagnosis. Published 2019. Accessed September 15, 2019. https://www.uptodate.com/contents/opioid-use-disorder-epidemiology-pharmacology-clinical-manifestations-course-screening-assessment-and-diagnosis#H134294385

708 Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. The Lancet. 2003;361(9358):662-668. doi:10.1016/S0140-6736(03)12600-1

709 Woody GE, Poole SA, Subramaniam G, et al. Extended vs Short-term Buprenorphine-Naloxone for Treatment of Opioid-Addicted Youth: A Randomized Trial. JAMA. 2008;300(17):2003-2011. doi:10.1001/jama.2008.574

References continued

710 Sigmon SC, Dunn KE, Saulsgiver K, et al. A Randomized, Double-blind Evaluation of Buprenorphine Taper Duration in Primary Prescription Opioid Abusers. JAMA Psychiatry. 2013;70(12):1347-1354. doi:10.1001/jamapsychiatry.2013.2216

711 Weiss RD, Potter JS, Provost SE, et al. A multi-site, two-phase, Prescription Opioid Addiction Treatment Study (POATS): Rationale, design, and methodology. Contemp Clin Trials. 2010;31(2):189-199. doi:10.1016/j.cct.2010.01.003

712 Rementeriá JL, Nunag NN. Narcotic withdrawal in pregnancy: stillbirth incidence with a case report. Am J Obstet Gynecol. 1973;116(8):1152-1156. doi:10.1016/0002-9378(73)90953-8

713 Zuspan FP, Gumpel JA, Mejia-Zelaya A, Madden J, Davis R. Fetal stress from methadone withdrawal. Am J Obstet Gynecol. 1975;122(1):43-46. doi:10.1016/0002-9378(75)90613-4

714 Jones HE, O'Grady KE, Malfi D, Tuten M. Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. Am J Addict. 2008;17(5):372-386. doi:10.1080/10550490802266276

715 Dashe JS, Jackson GL, Olscher DA, Zane EH, Wendel GD. Opioid detoxification in pregnancy. Obstet Gynecol. 1998;92(5):854-858. doi:10.1016/s0029-7844(98)00312-3

716 Luty J, Nikolaou V, Bearn J. Is opiate detoxification unsafe in pregnancy? J Subst Abuse Treat. 2003;24(4):363-367. doi:10.1016/s0740-5472(03)00035-7

717 Bell J, Towers CV, Hennessy MD, Heitzman C, Smith B, Chattin K. Detoxification from opiate drugs during pregnancy. Am J Obstet Gynecol. 2016;215(3):374.e1-6. doi:10.1016/j.ajog.2016.03.015

718 Macintyre PE, Russell RA, Usher K a. N, Gaughwin M, Huxtable CA. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. Anaesth Intensive Care. 2013;41(2):222-230. doi:10.1177/0310057X1304100212

719 Bentzley BS, Barth KS, Back SE, Book SW. Discontinuation of Buprenorphine Maintenance Therapy: Perspectives and Outcomes. J Subst Abuse Treat. 2015;52:48-57. doi:10.1016/j.jsat.2014.12.011

720 McCance-Katz, M.D., Ph.D. EF. Clinically Relevant Drug Interactions: Buprenorphine or Methadone with Other Frequently Prescribed Drugs. Providers Clinical Support System (PCSS) MAT Training. Published September 24, 2010. Accessed June 22, 2020. https://30qkon2g8eif8wrj03zeh041-wpengine.netdna-ssl.com/wp-content/uploads/2014/03/PCSSMAT-Clinically-Relevant-Drug-Interactions-Buprenorphine-or-Methadone-with-Other-Frequently-Prescribed-Drugs-9-24-101.pdf

721 McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict. 2010;19(1):4-16. doi:10.1111/j.1521-0391.2009.00005.x

722 McCance-Katz EF. Drug interactions associated with methadone, buprenorphine, cocaine, and HIV medications: implications for pregnant women. Life Sci. 2011;88(21-22):953-958. doi:10.1016/j.lfs.2010.09.016

723 Meyer M, Paranya G, Keefer Norris A, Howard D. Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. Eur J Pain Lond Engl. 2010;14(9):939-943. doi:10.1016/j.ejpain.2010.03.002

724 Ciraulo DA. Pharmacological Therapies for Drug and Alcohol Addictions. J Clin Psychopharmacol. 1996;16(2):194–195.

725 Cassidy B, Cyna AM. Challenges that opioid-dependent women present to the obstetric anaesthetist. Anaesth Intensive Care. 2004;32(4):494-501. doi:10.1177/0310057X0403200406

726 American Pyschiatric Association. Nearly One in Three People Know Someone Addicted to Opioids; More than Half of Millennials believe it is Easy to Get Illegal Opioids. Published May 7, 2018. Accessed September 12, 2019. https://www.psychiatry.org/newsroom/news-releases/nearly-one-in-three-people-know-someone-addicted-to-opioids-more-than-half-of-millennials-believe-it-is-easy-to-get-illegal-opioids.

727 Klie K, Brooks L. Opioid use in pregnancy: High risk and high reward. Colorado Medical Society. Published September 1, 2017. Accessed July 31, 2020. https://www.cms.org/articles/specialty-focus-obstetrics

728 ACOG Committee. ACOG Committee Opinion No. 363: patient testing: ethical issues in selection and counseling. Obstet Gynecol. 2007;109(4):1021-1023. doi:10.1097/01.AOG.0000263889.07297.d1

729 Johnson-Davis KL, Sadler AJ, Genzen JR. A Retrospective Analysis of Urine Drugs of Abuse Immunoassay True Positive Rates at a National Reference Laboratory. J Anal Toxicol. 2016;40(2):97-107. doi:10.1093/jat/bkv133

730 Janisse JJ, Bailey BA, Ager J, Sokol RJ. Alcohol, tobacco, cocaine, and marijuana use: relative contributions to preterm delivery and fetal growth restriction. Subst Abuse. 2014;35(1):60-67. doi:10.1080/08897077.2013.804483

731 Lloyd MH, Luczak S, Lew S. Planning for safe care or widening the net?: A review and analysis of 51 states' CAPTA policies addressing substance-exposed infants. Child Youth Serv Rev. 2019;99:343-354. doi:10.1016/j.childyouth.2019.01.042

732 Braillon A, Bewley S. Committee Opinion No. 722: Marijuana Use During Pregnancy and Lactation. Obstet Gynecol. 2018;131(1):164. doi:10.1097/AOG.0000000000002429

733 Quaility Improvement Resources. CHoSEN Collaborative. Accessed July 31, 2020. https://www.chosencollaborative.org/qi-resources.html

734 Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827-841. doi:10.1542/peds.2011-3552

735 Forray A, Merry B, Lin H, Ruger JP, Yonkers KA. Perinatal substance use: a prospective evaluation of abstinence and relapse. Drug Alcohol Depend. 2015;150:147-155. doi:10.1016/j.drugalcdep.2015.02.027

736 El-Mohandes AAE, El-Khorazaty MN, Kiely M, Gantz MG. Smoking cessation and relapse among pregnant African-American smokers in Washington, DC. Matern Child Health J. 2011;15 Suppl 1:S96-105. doi:10.1007/s10995-011-0825-6

References continued

737 Special Connections. Colorado Department of Health Care Policy and Financing. Published May 1, 2014. Accessed July 31, 2020. https://www.colorado.gov/pacific/hcpf/special-connections

738 Chapman SLC, Wu L-T. Postpartum substance use and depressive symptoms: a review. Women Health. 2013;53(5):479-503. doi:10.1080/03630242.2013.804025

739 Vestal C. Few Doctors Are Willing, Able to Prescribe Powerful Anti-Addiction Drugs. Published January 15, 2016. http://pew.org/1ZnFhSs

740 Auriacombe M, Fatséas M, Dubernet J, Daulouède J-P, Tignol J. French Field Experience with Buprenorphine. Am J Addict. 2004;13(S1):S17-S28. doi:10.1080/10550490490440780

741 Subbaraman MS, Thomas S, Treffers R, et al. Associations Between State-Level Policies Regarding Alcohol Use Among Pregnant Women, Adverse Birth Outcomes, and Prenatal Care Utilization: Results from 1972 to 2013 Vital Statistics. Alcohol Clin Exp Res. Published online June 18, 2018. doi:10.1111/acer.13804

742 Roberts SCM, Mericle AA, Subbaraman MS, et al. State Policies Targeting Alcohol Use during Pregnancy and Alcohol Use among Pregnant Women 1985-2016: Evidence from the Behavioral Risk Factor Surveillance System. Womens Health Issues Off Publ Jacobs Inst Womens Health. 2019;29(3):213-221. doi:10.1016/j.whi.2019.02.001

743 Bridges K. Race, Pregnancy, and the Opioid Epidemic: White Privilege and the Criminalization of Opioid Use During Pregnancy. Accessed July 31, 2020. https://harvardlawreview.org/2020/01/race-pregnancy-and-the-opioid-epidemic-white-privilege-and-the-criminalization-of-opioid-use-during-pregnancy/

744 Hosalli V, Ayyanagouda B, Hiremath P, Ambi U, Hulkund S. Comparative efficacy of postoperative analgesia between ultrasound-guided dual transversus abdominis plane and Ilioinguinal/Iliohypogastric nerve blocks for open inguinal hernia repair: An open label prospective randomised comparative clinical trial. Indian J Anaesth. 2019;63(6):450-455. doi:10.4103/ija.IJA_153_19

745 Klein SM, Pietrobon R, Nielsen KC, et al. Paravertebral Somatic Nerve Block Compared With Peripheral Nerve Blocks for Outpatient Inguinal Herniorrhaphy. Reg Anesth Pain Med. 2002;27(5):476-480. doi:10.1053/rapm.2002.35147

746 Batra RK, Krishnan K, Agarwal A. Paravertebral Block. J Anaesthesiol Clin Pharmacol. 2011;27(1):5-11.

747 Kang H, Kim B-G. Intravenous Lidocaine for Effective Pain Relief after Inguinal Herniorrhaphy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. J Int Med Res. 2011;39(2):435-445. doi:10.1177/147323001103900211

748 Oakley MJ, Smith JS, Anderson JR, Fenton-Lee D. Randomized placebo-controlled trial of local anaesthetic infusion in day-case inguinal hernia repair. Br J Surg. 1998;85(6):797-799. doi:10.1046/j.1365-2168.1998.00651.x

749 Lau H, Patil NG, Lee F. Randomized Clinical Trial of Postoperative Subfascial Infusion with Bupivacaine following Ambulatory Open Mesh Repair of Inguinal Hernia. Dig Surg. 2003;20(4):285-289. doi:10.1159/000071187

750 Schurr MJ, Gordon DB, Pellino TA, Scanlon TA. Continuous local anesthetic infusion for pain management after outpatient inguinal herniorrhaphy. Surgery. 2004;136(4):761-769. doi:10.1016/j.surg.2004.06.016

751 Gärtner R, Kroman N, Callesen T, Kehlet H. Multimodal prevention of pain, nausea and vomiting after breast cancer surgery. Minerva Anestesiol. 2010;76(10):805-813.

752 Hu L, Iannetti GD. Neural indicators of perceptual variability of pain across species. Proc Natl Acad Sci. 2019;116(5):1782-1791. doi:10.1073/pnas.1812499116

753 Hooten WM. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. Mayo Clin Proc. 2016;91(7):955-970. doi:10.1016/j.mayocp.2016.04.029

754 Shin LM, Liberzon I. The Neurocircuitry of Fear, Stress, and Anxiety Disorders. Neuropsychopharmacology. 2010;35(1):169-191. doi:10.1038/npp.2009.83

755 Doan L, Manders T, Wang J. Neuroplasticity Underlying the Comorbidity of Pain and Depression. Neural Plasticity. doi:https://doi.org/10.1155/2015/504691

756 Cánovas L, Carrascosa A-J, García M, et al. Impact of Empathy in the Patient-Doctor Relationship on Chronic Pain Relief and Quality of Life: A Prospective Study in Spanish Pain Clinics. Pain Med. 2018;19(7):1304-1314. doi:10.1093/pm/pnx160

757 Gleichgerrcht E, Decety J. The relationship between different facets of empathy, pain perception and compassion fatigue among physicians. Front Behav Neurosci. 2014;8. doi:10.3389/fnbeh.2014.00243

758 Xia N, Li H. Loneliness, Social Isolation, and Cardiovascular Health. Antioxid Redox Signal. 2017;28(9):837-851. doi:10.1089/ars.2017.7312

759 Wiech K. Deconstructing the sensation of pain: The influence of cognitive processes on pain perception. Science. 2016;354(6312):584-587. doi:10.1126/science.aaf8934

760 Alexander JC, Joshi GP. A review of the anesthetic implications of marijuana use. Bayl Univ Med Cent Proc. 2019;32(3):364-371. doi:10.1080/08998280.2019.1603034

761 Echeverria-Villalobos M, Todeschini AB, Stoicea N, Fiorda-Diaz J, Weaver T, Bergese SD. Perioperative care of cannabis users: A comprehensive review of pharmacological and anesthetic considerations. J Clin Anesth. 2019;57:41-49. doi:10.1016/j.jclinane.2019.03.011

762 Lopez-Quintero C, Cobos JP de los, Hasin DS, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. 2011;115(1):120-130. doi:10.1016/j.drugalcdep.2010.11.004

763 Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. The Lancet. 2009;374(9698):1383-1391. doi:10.1016/S0140-6736(09)61037-0

References continued

764 Stuyt E. The Problem with the Current High Potency THC Marijuana from the Perspective of an Addiction Psychiatrist. Mo Med. 2018;115(6):482-486.

765 Webb C. Marijuana Abuse: Increasing the Likelihood of the use of Harder Substances. Smart Approaches to Marijuana. Published February 11, 2019. https://learnaboutsam.org/guest-contribution-marijuana-abuse-increasing-the-likelihood-of-the-use-of-harder-substances/

766 Batalla A, Bhattacharyya S, Yücel M, et al. Structural and Functional Imaging Studies in Chronic Cannabis Users: A Systematic Review of Adolescent and Adult Findings. PLoS ONE. 2013;8(2). doi:10.1371/journal.pone.0055821

767 Filbey FM, Aslan S, Calhoun VD, et al. Long-term effects of marijuana use on the brain. Proc Natl Acad Sci. 2014;111(47):16913-16918. doi:10.1073/pnas.1415297111

768 Andréasson S, Engström A, Allebeck P, Rydberg U. CANNABIS AND SCHIZOPHRENIA A Longitudinal Study of Swedish Conscripts. The Lancet. 1987;330(8574):1483-1486. doi:10.1016/S0140-6736(87)92620-1

769 Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ. 2002;325(7374):1199. doi:10.1136/bmj.325.7374.1199

770 van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis Use and Psychosis: A Longitudinal Population-based Study. Am J Epidemiol. 2002;156(4):319-327. doi:10.1093/aje/kwf043

771 Henquet C, Krabbendam L, Spauwen J, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ. 2004;330(7481):11. doi:10.1136/bmj.38267.664086.63

772 Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002;325(7374):1212-1213. doi:10.1136/bmj.325.7374.1212

773 Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychol Med. 2003;33(1):15-21. doi:10.1017/S0033291702006402

774 Stefanis NC, Dragovic M, Power BD, Jablensky A, Castle D, Morgan VA. The effect of drug use on the age at onset of psychotic disorders in an Australian cohort. Schizophr Res. 2014;156(2):211-216. doi:10.1016/j.schres.2014.04.003

775 Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. The Lancet. 2007;370(9584):319-328. doi:10.1016/S0140-6736(07)61162-3

776 Libuy Hidalgo N, Angel V de, Ibáñez Berríos C, Murray RM, Mundt AP. The relative prevalence of schizophrenia among cannabis and cocaine users attending addiction services. Schizophr Res. Published online 2018. doi:10.1016/j.schres.2017.04.010

777 Di Forti M, Sallis H, Allegri F, et al. Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users. Schizophr Bull. 2014;40(6):1509-1517. doi:10.1093/schbul/sbt181

778 National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. National Academies Press (US); 2017. Accessed March 9, 2020. http://www.ncbi.nlm.nih.gov/books/NBK423845/

779 Lev-Ran S, Roerecke M, Foll BL, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol Med. 2014;44(4):797-810. doi:10.1017/S0033291713001438

780 Borges G, Bagge CL, Orozco R. A literature review and meta-analyses of cannabis use and suicidality. J Affect Disord. 2016;195:63-74. doi:10.1016/j.jad.2016.02.007

781 Wolff V, Zinchenko I, Quenardelle V, Rouyer O, Geny B. Characteristics and Prognosis of Ischemic Stroke in Young Cannabis Users Compared With Non-Cannabis Users. J Am Coll Cardiol. 2015;66(18):2052-2053. doi:10.1016/j.jacc.2015.08.867

782 Franz CA, Frishman WH. Marijuana Use and Cardiovascular Disease. Cardiol Rev. 2016;24(4):158–162. doi:10.1097/CRD.0000000000000103

783 Rumalla K, Reddy AY, Mittal MK. Association of Recreational Marijuana Use with Aneurysmal Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis. 2016;25(2):452-460. doi:10.1016/j.jstrokecerebrovasdis.2015.10.019

784 Rumalla K, Reddy AY, Mittal MK. Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. J Neurol Sci. 2016;364:191-196. doi:10.1016/j.jns.2016.01.066

785 Tashkin DP. Effects of Marijuana Smoking on the Lung. Ann Am Thorac Soc. 2013;10(3):239-247. doi:10.1513/AnnalsATS.201212-127FR

786 Moir D, Rickert WS, Levasseur G, et al. A Comparison of Mainstream and Sidestream Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions. Chem Res Toxicol. 2008;21(2):494-502. doi:10.1021/tx700275p

787 Wilson KM, Torok MR, Wei B, et al. Detecting biomarkers of secondhand marijuana smoke in young children. Pediatr Res. 2017;81(4):589-592. doi:10.1038/pr.2016.261

788 Gurney J, Shaw C, Stanley J, Signal V, Sarfati D. Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. BMC Cancer. 2015;15(1):897. doi:10.1186/s12885-015-1905-6

789 Liu C, Sadat SH, Ebisumoto K, et al. Cannabinoids promote progression of HPV positive head and neck squamous cell carcinoma via p38 MAPK activation. Clin Cancer Res. Published online January 1, 2020. doi:10.1158/1078-0432.CCR-18-3301

790 Fish EW, Murdaugh LB, Zhang C, et al. Cannabinoids Exacerbate Alcohol Teratogenesis by a CB1-Hedgehog Interaction. Sci Rep. 2019;9(1):1-16. doi:10.1038/s41598-019-52336-w

791 Bradford AC, Bradford WD. Medical Marijuana Laws May Be Associated With A Decline In The Number Of Prescriptions For Medicaid Enrollees. Health Aff (Millwood). 2017;36(5):945-951. doi:10.1377/hlthaff.2016.1135

References continued

792 Bradford AC, Bradford WD, Abraham A, Adams GB. Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population. JAMA Intern Med. 2018;178(5):667-672. doi:10.1001/jamainternmed.2018.0266

793 Segura LE, Mauro CM, Levy NS, et al. Association of US Medical Marijuana Laws With Nonmedical Prescription Opioid Use and Prescription Opioid Use Disorder. JAMA Netw Open. 2019;2(7):e197216-e197216. doi:10.1001/jamanetworkopen.2019.7216

794 Lucas PL. Cannabis as an Adjunct to or Substitute for Opiates in the Treatment of Chronic Pain. J Psychoactive Drugs. 2012;44(2):125-133. doi:10.1080/02791072.2012.684624

795 Ibrahim MM, Porreca F, Lai J, et al. CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. Proc Natl Acad Sci U S A. 2005;102(8):3093-3098. doi:10.1073/pnas.0409888102

796 Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. Life Sci. 2004;74(11):1317-1324. doi:10.1016/j.lfs.2003.09.038

797 Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. PAIN. 2018;159(10):1932–1954. doi:10.1097/j.pain.0000000000001293

798 Huestis MA. Human Cannabinoid Pharmacokinetics. Chem Biodivers. 2007;4(8):1770-1804. doi:10.1002/cbdv.200790152

799 Mikos R. Is CBD Legal Under Federal Law? – Marijuana Law, Policy, and Authority. Vanderbilt University Law School. Published September 28, 2018. Accessed March 6, 2020. https://my.vanderbilt.edu/marijuanalaw/2018/09/is-cbd-legal-under-federal-law/

800 American Medical Association. H-95.952 Cannabis and Cannabinoid Research. Accessed March 9, 2020. https://policysearch.ama-assn.org/policyfinder/detail/Cannabis?uri=%2FAMADoc%2FHOD.xml-0-5331.xml

801 Manzanares J, Corchero J, Romero J, Fernández-Ruiz JJ, Ramos JA, Fuentes JA. Pharmacological and biochemical interactions between opioids and cannabinoids. Trends Pharmacol Sci. 1999;20(7):287-294. doi:10.1016/S0165-6147(99)01339-5

802 Valverde O, Noble F, Beslot F, Daugé V, Fournié-Zaluski M-C, Roques BP. Δ9-tetrahydrocannabinol releases and facilitates the effects of endogenous enkephalins: reduction in morphine withdrawal syndrome without change in rewarding effect. Eur J Neurosci. 2001;13(9):1816-1824. doi:10.1046/j.0953-816x.2001.01558.x

803 Pacheco DDF, Klein A, Perez ADC, Pacheco CMDF, Francischi JND, Duarte IDG. The μ-opioid receptor agonist morphine, but not agonists at δ- or κ-opioid receptors, induces peripheral antinociception mediated by cannabinoid receptors. Br J Pharmacol. 2008;154(5):1143-1149. doi:10.1038/bjp.2008.175

804 Viganò D, Rubino T, Parolaro D. Molecular and cellular basis of cannabinoid and opioid interactions. Pharmacol Biochem Behav. 2005;81(2):360-368. doi:10.1016/j.pbb.2005.01.021

805 Cencioni MT, Chiurchiù V, Catanzaro G, et al. Anandamide Suppresses Proliferation and Cytokine Release from Primary Human T-Lymphocytes Mainly via CB2 Receptors. PLoS ONE. 2010;5(1). doi:10.1371/journal.pone.0008688

806 Woodhams SG, Sagar DR, Burston JJ, Chapman V. The role of the endocannabinoid system in pain. Handb Exp Pharmacol. 2015;227:119-143. doi:10.1007/978-3-662-46450-2_7

807 Hohmann AG, Briley EM, Herkenham M. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. Brain Res. 1999;822(1):17-25. doi:10.1016/S0006-8993(98)01321-3

808 Salio C, Fischer J, Franzoni MF, Mackie K, Kaneko T, Conrath M. CB1-cannabinoid and μ-opioid receptor co-localization on postsynaptic target in the rat dorsal horn. NeuroReport. 2001;12(17):3689–3692.

809 Walker JM, Hohmann AG, Martin WJ, Strangman NM, Huang SM, Tsou K. The neurobiology of cannabinoid analgesia. Life Sci. 1999;65(6):665-673. doi:10.1016/S0024-3205(99)00289-1

810 Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018;(3). doi:10.1002/14651858.CD012182.pub2

811 Pratt M, Stevens A, Thuku M, et al. Benefits and harms of medical cannabis: a scoping review of systematic reviews. Syst Rev. 2019;8(1):320. doi:10.1186/s13643-019-1243-x

812 Roberts BA. Legalized Cannabis in Colorado Emergency Departments: A Cautionary Review of Negative Health and Safety Effects. West J Emerg Med. 2019;20(4):557-572. doi:10.5811/westjem.2019.4.39935

813 Wang GS, Davies SD, Halmo LS, Sass A, Mistry RD. Impact of Marijuana Legalization in Colorado on Adolescent Emergency and Urgent Care Visits. J Adolesc Health. 2018;63(2):239-241. doi:10.1016/j.jadohealth.2017.12.010

814 Wang GS, Hall K, Vigil D, Banerji S, Monte A, VanDyke M. Marijuana and acute health care contacts in Colorado. Prev Med. 2017;104:24-30. doi:10.1016/j.ypmed.2017.03.022

815 Blanco C, Hasin DS, Wall MM, et al. Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence From a US National Longitudinal Study. JAMA Psychiatry. 2016;73(4):388-395. doi:10.1001/jamapsychiatry.2015.3229

816 Lorenzetti V, Lubman DI, Whittle S, Solowij N, Yücel M. Structural MRI Findings in Long-Term Cannabis Users: What Do We Know? Subst Use Misuse. 2010;45(11):1787-1808. doi:10.3109/10826084.2010.482443

817 Rocchetti M, Crescini A, Borgwardt S, et al. Is cannabis neurotoxic for the healthy brain? A meta-analytical review of structural brain alterations in non-psychotic users. Psychiatry Clin Neurosci. 2013;67(7):483-492. doi:10.1111/pcn.12085

818 Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Goudriaan AE. Grey matter alterations associated with cannabis use: Results of a VBM study in heavy cannabis users and healthy controls. NeuroImage. 2012;59(4):3845-3851. doi:10.1016/j.neuroimage.2011.09.046

819 Yücel M, Solowij N, Respondek C, et al. Regional Brain Abnormalities Associated With Long-term Heavy Cannabis Use. Arch Gen Psychiatry. 2008;65(6):694-701. doi:10.1001/archpsyc.65.6.694

References continued

820 Degenhardt L, Lintzeris N, Campbell G, et al. Experience of adjunctive cannabis use for chronic non-cancer pain: Findings from the Pain and Opioids IN Treatment (POINT) study. Drug Alcohol Depend. 2015;147:144-150. doi:10.1016/j.drugalcdep.2014.11.031

821 Reisfield GM, Wasan AD, Jamison RN. The Prevalence and Significance of Cannabis Use in Patients Prescribed Chronic Opioid Therapy: A Review of the Extant Literature. Pain Med. 2009;10(8):1434-1441. doi:10.1111/j.1526-4637.2009.00726.x

822 NSDUH State Estimates. Substance Abuse and Mental Health Data Archive (SAMHDA). Accessed July 31, 2020. https://pdas.samhsa.gov/saes/state

823 New York School of Regional Anesthesia. Thoracic and Abdominal Wall Blocks. Published 2020. https://www.nysora.com/techniques/truncal-and-cutaneous-blocks/

824 New York School of Regional Anesthesia. Upper extremity blocks. Published 2020. https://www.nysora.com/techniques/upper-extremity/

825 American Society of Regional Anesthesia and Pain Medicine (ASRA). Transversus Thoracic Plane Block: How I Do It. Published November 2019. https://www.asra.com/asra-news/article/214/transversus-thoracic-plane-block-how-i-d

826 Advancing the Science of Ultrasound Guided Regional Anesthesia and Pain Medicine (USRA). Links for Specific Blocks. http://www.usra.ca/regional-anesthesia/specific-blocks/home.php

827 Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med. 2010;35(1):64-101. doi:10.1097/aap.0b013e3181c15c70

828 Ghanavatian S, Derian A. Pudendal Nerve Block. In: StatPearls. StatPearls Publishing; 2020. Accessed July 17, 2020. http://www.ncbi.nlm.nih.gov/books/NBK551518/

829 Anderson D. Pudendal nerve block for vaginal birth. J Midwifery Womens Health. 2014;59(6):651-659. doi:10.1111/jmwh.12222

830 Davis JE. Paracervical block in obstetrics and gynecology. Calif Med. 1966;105(6):421-423.

831 Saloheimo AM. Paracervical block anesthesia in labor. Acta Obstet Gynecol Scand. 1968;47(S5):1-21. doi:10.3109/00016346809158479

832 Rosen MA. Paracervical block for labor analgesia: a brief historic review. Am J Obstet Gynecol. 2002;186(5 Suppl Nature):S127-130. doi:10.1067/mob.2002.121812

833 Eslamian L, Jalili Z, Jamal A, Marsoosi V, Movafegh A. Transversus abdominis plane block reduces postoperative pain intensity and analgesic consumption in elective cesarean delivery under general anesthesia. J Anesth. 2012;26(3):334-338. doi:10.1007/s00540-012-1336-3

834 Desai N, El-Boghdadly K, Albrecht E. Epidural vs. transversus abdominis plane block for abdominal surgery - a systematic review, meta-analysis and trial sequential analysis. Anaesthesia. Published online May 8, 2020. doi:10.1111/anae.15068

835 Kane SM, Garcia-Tomas V, Alejandro-Rodriguez M, Astley B, Pollard RR. Randomized trial of transversus abdominis plane block at total laparoscopic hysterectomy: effect of regional analgesia on quality of recovery. Am J Obstet Gynecol. 2012;207(5):419.e1-5. doi:10.1016/j.ajog.2012.06.052

836 De Oliveira GS, Milad MP, Fitzgerald P, Rahmani R, McCarthy RJ. Transversus abdominis plane infiltration and quality of recovery after laparoscopic hysterectomy: a randomized controlled trial. Obstet Gynecol. 2011;118(6):1230-1237. doi:10.1097/AOG.0b013e318236f67f

837 Kargar R, Minas V, Gorgin-Karaji A, et al. Transversus abdominis plane block under laparoscopic guide versus port-site local anaesthetic infiltration in laparoscopic excision of endometriosis: a double-blind randomised placebo-controlled trial. BJOG Int J Obstet Gynaecol. 2019;126(5):647-654. doi:10.1111/1471-0528.15502

838 Owen DJ, Harrod I, Ford J, Luckas M, Gudimetla V. The surgical transversus abdominis plane block--a novel approach for performing an established technique. BJOG Int J Obstet Gynaecol. 2011;118(1):24-27. doi:10.1111/j.1471-0528.2010.02779.x

839 Yoshiyama S, Ueshima H, Sakai R, Otake H. A Posterior TAP Block Provides More Effective Analgesia Than a Lateral TAP Block in Patients Undergoing Laparoscopic Gynecologic Surgery: A Retrospective Study. Anesthesiol Res Pract. 2016;2016:4598583. doi:10.1155/2016/4598583

840 McDonnell JG, O??Donnell B, Curley G, Heffernan A, Power C, Laffey JG. The Analgesic Efficacy of Transversus Abdominis Plane Block After Abdominal Surgery: A Prospective Randomized Controlled Trial: Anesth Analg. 2007;104(1):193-197. doi:10.1213/01.ane.0000250223.49963.0f

841 Belavy D, Cowlishaw PJ, Howes M, Phillips F. Ultrasound-guided transversus abdominis plane block for analgesia after Caesarean delivery. Br J Anaesth. 2009;103(5):726-730. doi:10.1093/bja/aep235

842 Blanco R, Ansari T, Girgis E. Quadratus lumborum block for postoperative pain after caesarean section: A randomised controlled trial. Eur J Anaesthesiol EJA. 2015;32(11):812–818. doi:10.1097/EJA.0000000000000299

843 Mieszkowski MM, Mayzner-Zawadzka E, Tuyakov B, et al. Evaluation of the effectiveness of the Quadratus Lumborum Block type I using ropivacaine in postoperative analgesia after a cesarean section - a controlled clinical study. Ginekol Pol. 2018;89(2):89-96. doi:10.5603/GP.a2018.0015

844 Kang W, Lu D, Yang X, et al. Postoperative analgesic effects of various quadratus lumborum block approaches following cesarean section: a randomized controlled trial. J Pain Res. 2019;12:2305-2312. doi:10.2147/JPR.S202772

845 VanderWielen B, Blanco R. ASRA News - Truncal Blocks for Cesarean Pain: Filling a Void in Obstetric Pain Management - American Society of Regional Anesthesia and Pain Medicine. Accessed July 31, 2020. https://www.asra.com/asra-news/article/56/truncal-blocks-for-cesarean-pain-filling

References continued

846 Atkins R. Quadratus lumborum block for elective cesarean section: simpler approach may gain more acceptance. Reg Anesth Pain Med. 2020;45(5):394-395. doi:10.1136/rapm-2019-101039

847 Krohg A, Ullensvang K, Rosseland LA, Langesæter E, Sauter AR. The Analgesic Effect of Ultrasound-Guided Quadratus Lumborum Block After Cesarean Delivery: A Randomized Clinical Trial. Anesth Analg. 2018;126(2):559-565. doi:10.1213/ANE.0000000000002648

848 Blanco R, Ansari T, Riad W, Shetty N. Quadratus Lumborum Block Versus Transversus Abdominis Plane Block for Postoperative Pain After Cesarean Delivery: A Randomized Controlled Trial. Reg Anesth Pain Med. 2016;41(6):757-762. doi:10.1097/AAP.0000000000000495

849 Sebbag I, Qasem F, Dhir S. [Ultrasound guided quadratus lumborum block for analgesia after cesarean delivery: case series]. Rev Bras Anestesiol. 2017;67(4):418-421. doi:10.1016/j.bjan.2017.03.002

850 Nair A. Bilateral quadratus lumborum block for post-caesarean analgesia. Indian J Anaesth. 2017;61(4):362-363. doi:10.4103/ija.IJA_204_17

851 Hansen CK, Dam M, Steingrimsdottir GE, et al. Ultrasound-guided transmuscular quadratus lumborum block for elective cesarean section significantly reduces postoperative opioid consumption and prolongs time to first opioid request: a double-blind randomized trial. Reg Anesth Pain Med. Published online July 14, 2019. doi:10.1136/rapm-2019-100540

852 Kerai S, Saxena KN. Quadratus lumborum block for post-caesarean analgesia. Indian J Anaesth. 2017;61(4):364. doi:10.4103/ija.IJA_220_17

853 Blanco R. Tap block under ultrasound guidance: the description of a “no pops” technique. Reg Anesth Pain Med. 2007;32(Suppl 1):130-130. doi:10.1136/rapm-00115550-200709001-00249

854 Jeong H-W, Kim CS, Choi KT, Jeong S-M, Kim D-H, Lee J-H. Preoperative versus Postoperative Rectus Sheath Block for Acute Postoperative Pain Relief after Laparoscopic Cholecystectomy: A Randomized Controlled Study. J Clin Med. 2019;8(7). doi:10.3390/jcm8071018

855 Takebayashi K, Matsumura M, Kawai Y, et al. Efficacy of Transversus Abdominis Plane Block and Rectus Sheath Block in Laparoscopic Inguinal Hernia Surgery. Int Surg. 2015;100(4):666-671. doi:10.9738/INTSURG-D-14-00193.1

856 Aveline C, Le Hetet H, Le Roux A, et al. Comparison between ultrasound-guided transversus abdominis plane and conventional ilioinguinal/iliohypogastric nerve blocks for day-case open inguinal hernia repair. BJA Br J Anaesth. 2011;106(3):380-386. doi:10.1093/bja/aeq363

857 Willschke H, Bösenberg A, Marhofer P, et al. Ultrasonographic-Guided Ilioinguinal/Iliohypogastric Nerve Block in Pediatric Anesthesia: What is the Optimal Volume? Anesth Analg. 2006;102(6):1680–1684. doi:10.1213/01.ane.0000217196.34354.5a

858 Willschke H, Marhofer P, Bösenberg A, et al. Ultrasonography for ilioinguinal/iliohypogastric nerve blocks in children. BJA Br J Anaesth. 2005;95(2):226-230. doi:10.1093/bja/aei157

859 Eichenberger U, Greher M, Kirchmair L, Curatolo M, Moriggl B. Ultrasound-guided blocks of the ilioinguinal and iliohypogastric nerve: accuracy of a selective new technique confirmed by anatomical dissection. BJA Br J Anaesth. 2006;97(2):238-243. doi:10.1093/bja/ael103

860 Gofeld M, Christakis M. Sonographically Guided Ilioinguinal Nerve Block. J Ultrasound Med. 2006;25(12):1571-1575. doi:10.7863/jum.2006.25.12.1571

861 Wolfson A, Lee AJ, Wong RP, Arheart KL, Penning DH. Bilateral multi-injection iliohypogastric-ilioinguinal nerve block in conjunction with neuraxial morphine is superior to neuraxial morphine alone for postcesarean analgesia. J Clin Anesth. 2012;24(4):298-303. doi:10.1016/j.jclinane.2011.09.007

862 Cooke CM, Flaxman T, Chen I, Singh SS. Ilioinguinal/iliohypogastric Nerve Blocks as a Treatment for Pelvic Pain in a Gynecologic Population [4R]. Obstet Gynecol. 2018;131:195S. doi:10.1097/01.AOG.0000533254.10572.12

863 Tsui BCH, Fonseca A, Munshey F, McFadyen G, Caruso TJ. The erector spinae plane (ESP) block: A pooled review of 242 cases. J Clin Anesth. 2019;53:29-34. doi:10.1016/j.jclinane.2018.09.036

864 Urits I, Charipova K, Gress K, et al. Expanding Role of the Erector Spinae Plane Block for Postoperative and Chronic Pain Management. Curr Pain Headache Rep. 2019;23(10):71. doi:10.1007/s11916-019-0812-y

865 El Ghamry MR, Amer AF. Role of erector spinae plane block versus paravertebral block in pain control after modified radical mastectomy. A prospective randomised trial. Indian J Anaesth. 2019;63(12):1008-1014. doi:10.4103/ija.IJA_310_19

866 Warrender WJ, Syed UAM, Hammoud S, et al. Pain Management After Outpatient Shoulder Arthroscopy: A Systematic Review of Randomized Controlled Trials. Am J Sports Med. 2017;45(7):1676-1686. doi:10.1177/0363546516667906

867 Altinpulluk EY, Ozdilek A, Colakoglu N, et al. Bilateral postoperative ultrasound-guided erector spinae plane block in open abdominal hysterectomy: a case series and cadaveric investigation. Romanian J Anaesth Intensive Care. 2019;26(1):83-88. doi:10.2478/rjaic-2019-0013

868 Frassanito L, Zanfini BA, Catarci S, Sonnino C, Giuri PP, Draisci G. Erector spinae plane block for postoperative analgesia after total laparoscopic hysterectomy: case series and review of the literature. Eur Rev Med Pharmacol Sci. 2020;24(7):3892-3897. doi:10.26355/eurrev_202004_20855

869 Rivedal DD, Nayar HS, Israel JS, et al. Paravertebral block associated with decreased opioid use and less nausea and vomiting after reduction mammaplasty. J Surg Res. 2018;228:307-313. doi:10.1016/j.jss.2018.03.018

870 El-Boghdadly K, Madjdpour C, Chin KJ. Thoracic paravertebral blocks in abdominal surgery – a systematic review of randomized controlled trials. Br J Anaesth. 2016;117(3):297-308. doi:10.1093/bja/aew269

References continued

871 Melnikov AL, Bjoergo S, Kongsgaard UE. Thoracic paravertebral block versus transversus abdominis plane block in major gynecological surgery: a prospective, randomized, controlled, observer-blinded study. Local Reg Anesth. 2012;5:55-61. doi:10.2147/LRA.S35858

872 Kirksey MA, Haskins SC, Cheng J, Liu SS. Local Anesthetic Peripheral Nerve Block Adjuvants for Prolongation of Analgesia: A Systematic Qualitative Review. PLoS ONE. 2015;10(9). doi:10.1371/journal.pone.0137312

873 Schäfer M, Mousa SA, Shaqura M, Tafelski S. Background and current use of adjuvants for regional anesthesia : From research to evidence-based patient treatment. Anaesthesist. 2019;68(1):3-14. doi:10.1007/s00101-018-0522-6

874 Bailard NS, Ortiz J, Flores RA. Additives to local anesthetics for peripheral nerve blocks: Evidence, limitations, and recommendations. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm. 2014;71(5):373-385. doi:10.2146/ajhp130336

875 Pehora C, Pearson AM, Kaushal A, Crawford MW, Johnston B. Dexamethasone as an adjuvant to peripheral nerve block. Cochrane Database Syst Rev. 2017;(11). doi:10.1002/14651858.CD011770.pub2

876 Chen Q, An R, Zhou J, Yang B. Clinical analgesic efficacy of dexamethasone as a local anesthetic adjuvant for transversus abdominis plane (TAP) block: A meta-analysis. PloS One. 2018;13(6):e0198923. doi:10.1371/journal.pone.0198923

877 Zhao W-L, Ou X-F, Liu J, Zhang W-S. Perineural versus intravenous dexamethasone as an adjuvant in regional anesthesia: a systematic review and meta-analysis. J Pain Res. 2017;10:1529-1543. doi:10.2147/JPR.S138212

878 Hussain N, Grzywacz VP, Ferreri CA, et al. Investigating the Efficacy of Dexmedetomidine as an Adjuvant to Local Anesthesia in Brachial Plexus Block: A Systematic Review and Meta-Analysis of 18 Randomized Controlled Trials. Reg Anesth Pain Med. 2017;42(2):184-196. doi:10.1097/AAP.0000000000000564

879 Reducing infections from injection drug use. Colorado Department of Public Health and Environment. Published October 19, 2017. Accessed June 22, 2020. https://www.colorado.gov/pacific/cdphe/reducing-infections-injection-drug-use

880 Substance Abuse and Mental Health Services Administration. Medications for Opioid Use Disorder: TREATMENT IMPROVEMENT PROTOCOL (TIP) 63 For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. Substance Abuse and Mental Health Services Administration. Published 2020. https://medicine.yale.edu/edbup/resources/TIP_63_338482_284_42920_v1.pdf

881 Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-Assisted Therapies — Tackling the Opioid-Overdose Epidemic. N Engl J Med. 2014;370(22):2063-2066. doi:10.1056/NEJMp1402780

882 Coffa M.D. D, Harter PharmD K, Smith M.D. B, Snyder M.D. H, Windels S. Inpatient Management of Opioid Use Disorder: Buprenorphine. Project SHOUT. Accessed June 24, 2020. https://static1.squarespace.com/static/5acbce828f51302409d8bdcb/t/5ad8279e758d464041d772d0/1524115363080/GUIDELINES+-+inpatient+buprenorphine+-+4-18-18.pdf

883 Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017;357:j1550. doi:10.1136/bmj.j1550

884 Hser Y-I, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addict Abingdon Engl. 2014;109(1):79-87. doi:10.1111/add.12333

885 Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. J Addict Dis. 2016;35(1):22-35. doi:10.1080/10550887.2016.1100960

886 Gibson A, Degenhardt L. Mortality Related to Naltexone in the Treatment of Opioid Dependence: A Comparative Analysis. National Drug & Alcohol Research Centre. Published 2005. Accessed June 25, 2020. https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/TR.229.pdf

887 Naltrexone. Substance Abuse and Mental Health Services Administration. Accessed July 31, 2020. https://www.samhsa.gov/medication-assisted-treatment/treatment/naltrexone

888 CaBridge Methadone Hospital Quick Start. BRIDGE - Treatment Starts Here. Accessed July 31, 2020. https://www.bridgetotreatment.org/resources