Optimizing Opioid Safety and Efficacy

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, nurses, pharmacists, and other healthcare professionals involved in the care of patients who may benefit from the use of opioids to address pain.

Accreditations & Approvals

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NetCE designates this continuing education activity for 15 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 15 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 18 hours for Alabama nurses.

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AACN Synergy CERP Category A.

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

This course fulfills the Michigan requirement for 2 hours of continuing education in pain and pain symptom management.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

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Course Objective

The purpose of this course is to provide clinicians with the information necessary to choose the appropriate opioid agents for their patients, with a resultant improvement in patients' quality of life and compliance with prescribed treatments.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define terms often used in discussion of opioid prescribing.
2. Analyze common myths related to opioid analgesic safety.
3. Recall the epidemiology of pain.
4. Outline the individual and societal impact of undertreated pain.
5. Describe risk factors for and comorbidities of chronic pain.
6. Evaluate barriers to adequate pain care.
7. Describe the endogenous opioid system and effects of opioid analgesia.
8. Discuss the classification and properties of the various mu opioid receptor full agonist agents.
9. Compare and contrast other types of opioid analgesics and antagonists.
10. Identify pharmacokinetic factors in opioid analgesic response.
11. Outline the Centers for Disease Control and Prevention's (CDC's) guidelines for opioid prescribing for chronic pain.
12. Recall other general recommendations for safe and effective long-term opioid use for chronic pain.
13. Identify patient factors that affect opioid analgesic response.
14. Describe issues that affect choices regarding opioid selection, rotation, and titration.
15. Discuss the identification and appropriate treatment of opioid analgesic side effects.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the scope and impact of pain, including risk factors, barriers to care, and myths.
2. Describe various opioid medications, the impact on the body, and their role in the treatment of pain.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Opioid analgesics are approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate or severe pain. However, individual patients differ greatly in clinical response (e.g., efficacy, side effects, safety) to different opioid analgesics, and patient populations show widely variable response to the same opioid and dose [1]. These response variations make opioid prescribing challenging. Scientific advances have improved the understanding of how opioid response is conditioned by genetic factors, comorbidity, drug interactions, and opioid dynamics and/or kinetics. Informed health professionals are now better able to match patients with a selected treatment option to maximize safety, efficacy, and tolerability when prescribing opioid analgesics.

The important role of opioid analgesics is broadly accepted in acute pain, cancer pain, and palliative and end-of-life care, but it is controversial for the management of chronic noncancer pain [2]. In recent years, the climate surrounding opioid analgesics has become decidedly negative, a response to the excessive prescribing and increases in fatal overdose during the 2000s. This backlash has prompted concerted broadcasting of opioid analgesic public health hazards, culminating in the 2016 Centers for Disease Control and Prevention (CDC) opioid prescribing guidelines that focus on curtailing prescribing and patient access [3; 4]. However, guidance on improving prescription opioid analgesia and tolerability by carefully matching the patient to the selected opioid, unaddressed in the CDC guidelines, is also essential for effective treatment of pain [5; 6].

Prescription opioid analgesic use and overdose both appear to be in multi-year declines from their 2011 peak. This course will provide perspective and address common misperceptions of opioid analgesic safety and potential benefits in order to help establish the basis for a balanced risks/benefits

discussion and convey that with appropriate due diligence, opioid analgesics can be prescribed safely to benefit patients in pain who lack response to, or are unlikely to benefit from, other analgesics [7; 268].

Opioids are not a panacea for pain, nor are they safe and effective for every patient. However, they can be a useful tool, and knowledge of medical advances can give clinicians greater confidence to safely and effectively prescribe these drugs. In this course, chronic pain management is emphasized because the potential patient/opioid interactions are more complex and current guidance can be enhanced. Unless stated otherwise, this course focuses on noncancer pain.

DEFINITIONS

Acute pain: Pain from tissue injury that resolves with tissue healing [16]. Acute pain may be protracted without mechanistic conversion to chronic pain, resolving with treatment [17].

Addictive drug: A disproven concept that some drugs are inherently "addictive." Addiction results from individual susceptibility and not from a substance. Most people do not respond with addictive behavior when prescribed opioids with abuse potential, while predisposed persons may abuse any opioid analgesic [9; 10; 11].

Analgesic tolerance: Diminished or lost analgesia requiring dose titration to regain pain relief. A concerning complication in long-term opioid therapy, long-term trials of transdermal fentanyl or extended-release (ER) oxycodone suggest analgesic tolerance is much less frequent and clinically relevant than previously believed [8].

Centralized pain: Refers to peripheral and central sensitization without detectable peripheral origin and includes fibromyalgia, irritable bowel syndrome, and tension-type headache. Also known as dysfunctional pain.

Central sensitization: The process by which pain initially generated from peripheral injury becomes embedded in the central nervous system (CNS) through pathologic adaptation to become self-perpetuating and amplified, uncoupled from original tissue origin, very difficult to treat, and potentially intractable [19].

Chronic pain: Pain lasting longer than three months or longer than expected healing time. Previously, chronic pain has been conceptualized as merely the continuation of acute pain beyond a chosen temporal cut-off point, a notion now considered overly simplistic. The transition from acute to chronic pain is now understood to involve a shift in pathogenic mechanisms from that associated with early-phase tissue injury and healing to a later period of abnormal, maladaptive sensory processing and neuronal plasticity that develops within peripheral and central pain pathways. Importantly, psychologic status, cultural background/beliefs, and relationships/interactions in the workplace, home, and healthcare environments contribute to development and persistence of chronic pain [18].

Inflammatory pain: Nociceptive pain with a localized immune response that generates proinflammatory mediators to facilitate tissue repair.

Neuropathic pain: Originates from injury to specific peripheral nervous system (PNS) or CNS structures or to all peripheral sensory nerves (e.g., with diabetes or postherpetic neuralgia).

Neuroplasticity: The capacity of nerve cells to adapt and regenerate.

Nociceptive pain: The normal acute response to peripheral tissue injury or damage.

Pain: Physical discomfort. Pain is classified into four types (nociceptive, inflammatory, neuropathic, and centralized); chronic pain usually involves multiple pain mechanisms [13; 14; 15].

Pseudoaddiction: An iatrogenic condition whereby patients display drug-seeking behaviors mimicking opioid use disorder but driven by intense need for pain relief. Resolves with adequate pain control [12].

OPIOID ANALGESIC SAFETY, RISKS, AND BENEFITS: FACTS VERSUS FALLACIES

Safety considerations are the foundation of opioid analgesic prescribing, reflecting the basic principles of good medical practice [20]. As such, any comprehensive review of opioid analgesic therapy should address the assumptions that surround opioid analgesic prescribing for pain.

From the late 1990s through 2011, opioid analgesic prescribing and fatal overdose greatly increased [21]. The CDC identified this pattern, and their prompt attention and broadcasting elevated physician and public awareness and assisted in closing "pill mills" that served as conduits for millions of opioid doses into illicit markets [3]. The reaction to opioid overprescribing and overdose prompted efforts to curtail opioid prescribing, in part, by swaying physician and public opinion against opioids [6; 7; 22; 23; 24]. As of 2018, the total volume of opioid prescriptions nationally has dropped more than 40% from its level in 2011 [268]. This section addresses common misperceptions about opioid analgesics.

PRESCRIPTION OPIOID ANALGESIC FATAL OVERDOSE RATES

There is a misperception that overdose deaths from legally obtained prescription opioid analgesics continue rising, perpetuating an opioid epidemic. In fact, prescription opioid analgesic overdose deaths have steadily declined since 2012.

This perception is in part the result of CDC data indicating 18,893 prescription opioid overdose deaths in 2014, up sharply from 16,300 deaths in 2013 [26]. However, the 2014 increase was the result of a change in reporting standards. Starting in early 2014, the CDC began classifying all fentanyl overdoses as prescription opioid analgesic deaths, because laboratory tests were unable to distinguish clandestine from pharmaceutical fentanyl [27]. Also in 2014, there was an influx of fentanyl into the illicit opioid market, largely from Mexico and often sold as heroin or oxycodone. This resulted in a significant increase in fentanyl overdose deaths.

However, the total number of prescribed fentanyl dose units in 2014 (6.7 million) and 2013 (6.8 million) was unchanged [29]. In 2016, the CDC stated that the increase in overdose deaths in 2014 was mainly from adding fentanyl overdoses, almost all from clandestine fentanyl [28]. The CDC also provided an adjusted 2014 estimate (14,000 opioid overdose deaths), which was a continued decrease from the prescription opioid analgesic overdose deaths peak in 2011 (16,917 deaths) [30].

In 2018, there were 67,367 drug overdose deaths in the United States, a 4.1% decline from 2017 [269]. Of the total, 46,802 deaths (69.5%) involved some form of opioid. While deaths involving synthetic opioids increased 10%, driven largely by illicitly manufactured fentanyl and fentanyl analogs, the age-adjusted rate of drug-overdose deaths involving natural and semisynthetic prescription opioids (such as morphine, codeine, hydrocodone, and oxycodone) declined 13.5%, from 4.4 per 100,00 population in 2017 to 3.8 in 2018 [270].

It should also be noted that heroin overdose deaths are often undercounted, and morphine deaths overcounted, because heroin rapidly metabolizes into morphine. Many medical examiners are reluctant to label a death heroin-related without 6-monoaceytlmorphine present. However, this metabolite, unique to heroin, quickly metabolizes into morphine. The actual figures of heroin overdose reported as morphine are unknown, but when heroin overdose deaths increase, morphine overdose deaths also tend to increase [31].

PRESCRIPTION OPIOID ANALGESIC PRESCRIBING RATES

Many healthcare professionals believe that continued increases in opioid analgesic prescribing are fueling the opioid epidemic. In fact, the prescription rates of several opioid products are in multi-year declines. Total dispensed opioid prescriptions decreased 4.5% between 2011 and 2014, despite increases in tramadol (25.5%) and buprenorphine (49.4%) prescribing rates [29].

In late 2010, oxycodone ER was introduced as an abuse-deterrent formulation (ADF) to reduce abuse and overdose. After this product was released, there was a 39% prescribing decrease between 2010 and late 2012 [32]. In addition, oxycodone "doctor shopping" decreased 50% and overdose fatalities reported to the manufacturer decreased 65% [33].

Though it is still early, hydrocodone/acetaminophen combination product prescribing appears to be decreasing after it was rescheduled as a Schedule II controlled substance in 2014. After one year, there were 26.3 million fewer (-22%) prescriptions and 1.1 billion fewer (-16%) dispensed tablets [34]. Decreased hydrocodone/acetaminophen prescribing by primary care physicians during this period is also notable, with a 33% decrease from 2011 (144.5 million) to 2015 (97 million) [29; 35; 36].

After a steady increase in the overall national opioid prescribing rate starting in 2006, the total number of prescriptions dispensed peaked and leveled off in 2010–2012 at more than 255 million annually and a prescribing rate of 81 prescriptions per 100 persons. The opioid prescribing rate declined from 2012 to 2018, and in 2018, the prescribing rate had fallen to the lowest in 13 years, totaling 168 million opioid prescriptions (51 prescriptions per 100 persons) [217].

While it is true that the United States uses 99% of global hydrocodone, this is partially due to the fact that the few countries with adequate opioid access prefer dihydrocodeine or low-dose morphine for moderate/moderately severe pain [37]. Liberal opioid analgesic prescribing in some European countries has not led to the addiction and overdose rates seen in the United States, which reflects contribution from uniquely American factors beyond opioid analgesic exposure [38; 39; 40].

PRESCRIPTION OPIOID ANALGESICS AND HEROIN

The use of prescription opioid analgesics has long been proposed as a "gateway" to heroin. However, progression from opioid prescription misuse to heroin initiation is infrequent. Among non-medical users of opioid analgesics, 3.6% initiate heroin use within five years of initial abuse of prescription opioids [41]. Although most persons who misuse opioids do not progress to heroin use, it is also true that the majority of current heroin users initially misused prescription opioids.

EVIDENCE OF LONG-TERM OPIOID BENEFIT FOR CHRONIC PAIN

No analgesic used for the treatment of chronic pain (opioid or other class) has evidence of long-term safety and efficacy from randomized controlled trials lasting longer than one year [39]. Although this has been used to support the belief that opioids are unsafe for prolonged treatment of chronic pain, this level of evidence is lacking for any analgesic drug in use for chronic pain [30; 39; 42]. Thus, the absence of evidence is not evidence of absence [5; 44]. Many non-randomized controlled trials of opioid analgesics lasting one year or longer have substantive clinical value.

In general, opioid and other analgesic drug trials are seldom longer than 12 weeks in duration, and many obstacles interfere with the ability to conduct long-term opioid trials [45; 46]. First, ethical standards prohibit randomizing 50% of subjects in substantial pain to placebo. In addition, complexity and expense deter researchers from using active-drug controls in randomized controlled trials; these trials are unattractive to industry funding. There are also very high dropout rates of subjects with chronic pain randomized to placebo.

Several factors make analgesic efficacy of opioid analgesics difficult to demonstrate in tightly controlled randomized trials [8; 44; 45]. Studies report average opioid response of large patient numbers under rigid, predetermined starting dose and titration. However, opioid response in chronic pain is bimodal and not normally distributed; patients primarily show substantial or negligible analgesic response. When individual patient response is pooled and averaged, modest benefit is reported.

The strict, inflexible dosing parameters in randomized controlled trials lead to high dropout rates from analgesic failure or intolerability. This underestimates efficacy and overestimates toxicity. Many such patients would gain analgesia and tolerability using an approach tailored to patient factors that influence opioid response.

PRIMARY CONTRIBUTORS TO OPIOID ANALGESIC-RELATED FATALITIES

Misuse or abuse of prescribed opioid analgesics may account for a smaller proportion of poisoning overdoses than assumed. Data from Florida during 2007–2013 found 12% of 5,254 patients treated for non-fatal prescription opioid overdose in Broward County were diagnosed with opioid use disorder; 88% were legally prescribed users without diagnosable opioid use disorder [55]. These findings suggest prescription opioid abuse may be a less frequent cause of overdose than commonly assumed.

Studies show that the majority of opioid analgesic deaths stem from combining opioids with sedative hypnotics and/or alcohol [6; 47]. The extent to which contributing factors drive overdose rates is a more complex problem.

Methadone

Methadone analgesic prescribing began in the late 1990s [48]. In 1999, 784 overdose deaths were attributed to methadone. By 2011, this number increased to 4,418 (26% of opioid analgesic deaths) [48]. Factors that have contributed to increased methadone deaths include prescriber knowledge deficits of its complex pharmacology and its designation by insurer/third-party payers as the first-line chronic pain drug on the sole basis of cost savings [7; 49; 50].

Benzodiazepines

Benzodiazepines contribute to a significant number of opioid analgesic deaths, particularly with higher-dose opioid prescribing [47]. In 2011, benzodiazepines were associated with 31% of opioid analgesic fatalities, compared with 18.4% in 2004 [51]. However, this 2011 figure may understate the true benzodiazepine contribution. In a study of 607,156 people 15 to 64 years of age, 84.5% of those prescribed opioids for pain who died of opioid analgesic overdose were co-prescribed benzodiazepines [52]. In another study of more than 2 million North Carolina residents receiving one or more opioid analgesics, benzodiazepines were present in 61.4% who fatally overdosed. The potential role of other psychoactive substances used in combination with prescription opioids was further examined using data from the National Multiple-Cause-of-Death Files for the periods 2002–2003 and 2014–2015. This study showed that among persons dying of opioid analgesic overdose the most frequent combination was with benzodiazepines [60]. Furthermore, the proportion of opioid overdose deaths in combination with benzodiazepines increased from 16.8% in 2002–2003 to 27.9% in 2014–2015 in spite of the fact, as noted, that the opioid prescribing rate had been declining during the latter period.

Alcohol

Alcohol coingestion may also contribute to opioid analgesic-related deaths. In 2010, 20% of opioid overdose deaths involved alcohol [53].

Prescriber Knowledge Deficits

Studies indicate that fatal respiratory depression events often occur in the first five days of initial opioid therapy, with most in the initial 24 hours. This reflects initiation of therapy at too high a starting dose or failure to consider other risk factors, such as co-prescribed CNS sedatives [54].

EPIDEMIOLOGY OF PAIN

Persistent pain has been reported to affect one in three adults in the United States and to cost more than $600 billion annually [2]. In 2011, the Institute of Medicine (IOM) estimated that more than 100 million Americans suffer from persistent or chronic pain, with roughly 10% experiencing chronic, disabling pain [2]. The CDC analyzed data from the 2016 National Health Interview Survey to determine a more current and precise estimate of the prevalence of chronic pain in the United States, where chronic pain was defined as pain on most days or every day in the past six months. Based on this survey, an estimated 50 million adults experience chronic pain, with 19.6 million reporting high impact pain that limits life or work activities on most days [43]. These estimates indicate that chronic pain is experienced by 20% to 30% of adults in the United States, similar to the rates reported in Canada, Australia, and European countries.

Pain is a leading cause of chronic illness in persons older than 60 years of age, a major cause of disability, and the cardinal feature of arthritis, migraine, cancer, metabolic disorders, and neuropathies. Pain control in these diseases is notoriously difficult and often requires opioids [61; 62]. Neuropathic pain, which includes diabetic neuropathy, complex regional pain syndrome, radiculopathy, phantom limb pain, human immunodeficiency virus (HIV) sensory neuropathy, multiple sclerosis-related pain, and post-stroke pain, affects 5% to 10% of the U.S. population [63].

Chronic pain prevalence varies by subgroup. In general, older adults have a much greater prevalence than younger adults. Higher rates of chronic pain are found among those living in poverty, in women, those recently hospitalized, obese individuals, and those who never graduated high school [43]. Roughly 50% of adults rating their health as fair or poor suffer from chronic pain [64].

Chronic pain rates are likely to continue increasing as the population ages and more people develop pain-associated conditions such as obesity, diabetes, cardiovascular disorders, arthritis, and cancer. Other contributors to chronic pain include improved trauma care (with more surviving with chronic pain), the increase in surgical procedures, and greater public understanding of chronic pain and access to health insurance [2].

The most common anatomic locations of pain in U.S. adults are the low back (28.1%), knee (19.5%), severe headache or migraine (16.1%), neck (15.1%), shoulder (9.0%), finger (7.6%), and hip (7.1%). The lifetime prevalence of spinal pain ranges from 54% to 80% [2]. In patients with low back pain or neck pain, 25% to 60% report pain lasting longer than one year from onset; high pain and disability levels were found in 23% of patients with low back pain and 15% of patients with neck pain. Low back pain is linked to greatest declines in function and quality of life [65].

As noted, adult women have an overall higher prevalence of chronic pain than men [66]. Some chronic pain syndromes occur only, or predominantly, in women, including chronic fatigue syndrome, endometriosis, fibromyalgia, interstitial cystitis, vulvodynia, and temporomandibular disorders. Roughly 50 million women have one or more of these conditions, which frequently co-occur [2].

CONSEQUENCES OF UNTREATED OR UNDERTREATED CHRONIC PAIN

Pain is a distressing sensory and emotional experience for the patient, imposing potentially life-altering physiologic, psychosocial, and quality of life alterations [2]. The negative impact of chronic pain on quality of life is more severe than heart failure, renal failure, or major depression and comparable to terminal cancer [67; 68].

Failure to manage pain has serious pathophysiologic consequences, including cardiovascular (hypertension, myocardial ischemia, cardiovascular collapse) and physiologic (appetite loss, failure to thrive, immune dysfunction, endocrine failure) consequences, suppression of physical activity leading to joint and muscle deterioration, chronic sleep disturbance, dementia, and premature death [2; 13; 69]. Among 6,940 primary care patients followed over 10 years, those with poorly controlled moderate-to-severe chronic pain had a 68% greater risk of death than those with cardiovascular disease and 49% greater risk than all other causes combined [70].

Psychosocial consequences of unmanaged pain can be severe, with adverse psychologic (impaired cognitive function, pathologic anxiety/depression, suicidal ideation, despair, hopelessness) and social/interpersonal (relationship disruption, loss of employment, financial difficulties) outcomes [2; 13; 71; 72; 73]. Chronic pain is second only to bipolar disorder as a medical cause of suicide [74; 75; 76].

Chronic undercontrolled pain activates CNS glial cells and leads to neuroinflammation, tissue destruction, loss of CNS tissue mass and receptors, and unresponsiveness to usual-dose opioids and other analgesics. These patients often require higher-dose opioids; the modest analgesic response can reduce suffering and prevent suicide [77].

Negative attitudes by primary care providers and other clinicians toward patients with chronic pain who use/misuse illicit or prescription drugs are widespread, with hedonistic pursuit the assumption. Reality may be more complex, as patients with chronic pain potentially use substances to alleviate poorly controlled pain. This was explored in a study of adult primary care clinic patients who tested positive for illicit drug use or prescription drug misuse. Of the 589 patients [78]:

- 87% reported chronic pain (13% mild, 24% moderate, 50% severe)
- 74% reported impairment from pain (15% mild, 23% moderate, 36% severe)
- 51% of those who used illicit drugs (cannabis, heroin) stated they did so to treat pain
- 81% of those who misused prescription drugs stated they did so to self-medicate pain
- 38% of those who reported past three month heavy drinking stated they did so to treat pain

Chronic pain and impairment from pain were the norm in primary care patients with positive drug screens. Nearly one-third reported both severe pain and disabling impairment. This study suggests that poor pain control is common, apparent substance use disorder may reflect pseudoaddiction, and pain requires attention in patients counseled about their substance use [78].

RISK FACTORS FOR CHRONIC PAIN

PSYCHOSOCIAL RISK FACTORS

Intense persistent pain and persistent emotional distress are both powerful physiologic stressors that activate the hypothalamic-pituitary-adrenal (HPA) axis, the body's primary stress-control mechanism. The HPA axis becomes dysregulated from prolonged activation, causing a cascading effect that activates immune and inflammatory factors and glutamate receptor complex elements [69]. Neuroplasticity, the alteration in activity and function of synapses and neuronal networks, mediates the development, chronicity, and treatment resistance of pain and psychiatric conditions through diminished neurogenesis, synaptic deficits, decreased neurotrophic factors (e.g., brain-derived neurotrophic factor), and dendritic pathology [79]. Neuroplastic changes lead to central sensitization and hyperalgesia in patients with chronic pain and in patients with major depression even when ongoing pain is absent [80].

Abuse and Trauma

Early childhood trauma greatly influences experiences of pain, and childhood physical and sexual abuse negatively and independently influences adult health status, even after controlling for psychiatric disorders [66]. Abuse in childhood strongly predicts depression and pain in adulthood, and childhood sexual abuse highly predicts later chronic pain.

Childhood trauma stimulates the release of inflammatory cytokines and the development of central sensitization, greatly elevating later risks of immune, endocrine, and nervous system dysregulation [81]. Adults with depression and a history of childhood abuse show amplified stress response and altered adrenocorticotropic hormone and cortisol release. Glucocorticoid receptor dysfunction and downregulation is a bidirectional cause/effect of abnormal HPA-axis regulation in patients with depression [82]. Neuroinflammation is the common mediator of comorbid chronic pain and depression [83].

Coping and Social Support

Multiple psychologic mechanisms can alter pain outcomes and facilitate the progression of acute pain to chronic pain. Pain tolerance is adversely affected by mood, and factors such as pain coping skills and social support can affect pain and functionality [84; 85]. Low socioeconomic status, characterized in part by lower education level and inequality in healthcare access, also correlates with chronic pain [66].

The presence of maladaptive coping styles such as catastrophizing, kinesophobia (i.e., fear of movement), and somatization (i.e., emotional distress expressed through physical symptoms) predicts development of chronic pain [65]. Craving is strongly associated with drug misuse in patients prescribed opioids for chronic pain, and pain catastrophizing is associated with craving even after controlling for demographic, psychologic, medical, and medication regimen variables. This underscores the importance of including psychologic interventions in the overall pain care [86].

Passive avoidant behavioral patterns, lack of engagement in self-care, and job dissatisfaction also elevate the risk of chronic pain [87; 88]. Emotions and expectancies are strongly linked; negative emotions are associated with a generalized expectation of negative outcomes. The goal to avoid pain is often pursued with concurrent and often competing goals. Patients with chronic pain frequently weigh the value of pain avoidance against the costs related to loss of desired activities [84].

Neurobiologic mediation of social pain overlaps with physical pain. Social exclusion, bullying, isolation, and lack of support cross-sensitizes and amplifies physical pain. This relationship is bidirectional and highly relevant to patients with chronic pain who commonly encounter a process of rejection and social separation [66]. Passive pain coping and low levels of social support predict functional disability in patients with arthritis-related pain [89].

Addressing coping skills and bolstering social support can improve long-term pain outcomes and mitigate problematic medication use [85]. Patients with chronic pain and a history of prescription opioid use disorder who do not abuse their prescribed opioids are more likely to be active members of 12-step groups and have stable support systems [90].

MEDICAL RISK FACTORS

Obesity

Obesity is a pro-inflammatory state, and adipose tissue releases inflammatory mediators that increase chronic pain risks. Increased body weight and joint load can also promote or exacerbate painful conditions such as osteoarthritis [91].

Past Surgeries

Of patients undergoing surgery, 10% to 50% experience persistent pain and 2% to 10% experience severe pain. Inadequately treated postsurgical acute pain is common and increases the risk for developing chronic pain [2]. Chronic pain develops after thoracic surgery in 25% to 60% of patients and after herniorrhaphy in 14% [85].

COMMON COMORBID CONDITIONS

Major Depressive Disorder and Anxiety Disorders

Major depressive disorder is the single most important and prevalent chronic pain comorbidity. It is difficult to treat and renders pain control nearly impossible; anhedonia (i.e., inability to feel pleasure) is a frequent symptom [8; 66]. Primary care patients with muscle pain, headache, or stomach pain complaints are 2.5 to 10 times more likely to have diagnosable panic disorder, generalized anxiety disorder, or major depressive disorder than those without pain. Patients whose pain level results in work interference show elevated risk of panic disorder and major depressive disorder. Conversely, major depressive disorder increases the odds of muscle pain complaints, headache, stomach pain, and pain interference with daily functioning. These results reflect the complex interaction between pain and medical/psychiatric comorbidities [92].

Sleep Impairment

Disturbed phase 2/3 and rapid eye movement sleep decreases pain threshold, impairs immune function, decreases insulin sensitivity, and undermines pain treatment response. Roughly 50% to 70% of patients with chronic pain experience sleep disturbance, and pain, sleep, and mood are connected and mutually reinforcing—sleep disturbance exacerbates pain, and pain disrupts sleep. The bidirectional association results from lowered pain threshold, promotion of hyperalgesia, and increased release of inflammatory cytokines [8; 93]. Sleep recovery has an analgesic effect [85].

Medical Comorbidity

The presence of chronic pain is substantially elevated in patients with chronic respiratory disease, cardiovascular disease, or neurologic, metabolic, endocrine, and gastrointestinal (GI) disorders [94]. Among multi-morbid primary care patients older than 65 years of age, chronic low back pain was the most prevalent pain condition, significantly associated with cardiometabolic conditions in both sexes and depression in women [95].

BARRIERS TO ADEQUATE PAIN CARE

Pain arises in the nervous system but represents a complex, evolving interaction of biologic, behavioral, environmental, and societal factors. Biopsychosocial factors greatly influence pain perception, persistence, and treatment outcomes in patients with chronic pain [2]. As such, a coordinated multimodal approach with pharmacopoeia, cognitive-behavioral or other coping skills therapy, and a progressive strengthening or functional restoration modality is recommended [96; 97]. Despite substantially greater efficacy than uncoordinated symptomatic care, few patients with chronic pain receive multidisciplinary pain care [85].

Chronic pain affects all domains of life, and clinicians have few effective tools at their disposal to help these patients [98]. Opioids remain the strongest group of analgesic drugs available [99]. Millions of patients are safely and effectively maintained on relatively high-dose opioids for chronic, severe pain and require these medications to function. Public pressure and the mischaracterization of patients as "drug addicts" has increasingly deterred prescribers from treating patients with chronic pain successfully managed with opioids for years or decades rather than improving safety practices [22; 100]. However, opioids, like many medications, have serious risks and should not be treated like a cure-all [56]. This dichotomy has resulted in many patients for whom opioid analgesics are appropriate increasingly experiencing barriers to pain relief.

The IOM has stated that the uncertain diagnosis in many chronic pain cases, combined with stigma toward patients in pain, interferes with treatment seeking and adherence to follow-up. Negative provider interactions are powerful deterrents to future help-seeking by adults with chronic pain, particularly the elderly. Patient perception of having their pain complaint dismissed or of not being listened to by their initial pain provider can discourage subsequent care seeking or result in changing providers [2].

These observations are echoed by the National Pain Strategy (NPS), adding that in addition to prevalent stigma, increasing reluctance of many clinicians to prescribe opioids jeopardizes adequate pain control for patients with chronic pain. For most pain conditions, medications (including opioids) may be essential for improved quality of life, and rationing, medication shortages, and inadequate reimbursement decreases patients' access to medications, causing considerable hardship in this vulnerable population [101].

At greatest risk of unrelieved pain from stigma and bias are children, the elderly, racial and ethnic minorities, active duty or military veterans, and those with cancer, HIV, or sickle cell disease. Pain undertreatment in black patients is especially widespread, from prevalent misperceptions that this group has higher pain tolerance and is more likely to abuse their opioid prescription [102].

The CDC guideline recommends that pain specialists, not primary care providers, manage patients requiring >90 mg daily morphine equivalent dosage (MED), but this is often unrealistic in practice. The number of pain specialists is inadequate to manage the large number of patients with pain severity and disability that requires >90 mg MED. Patients may feel abandoned or panicked about the potential loss of effective pain control. Adherence to this recommendation can therefore have potentially serious consequences for patients requiring opioids, and the growing problem of opioid medication access is likely to worsen [56].

THE ENDOGENOUS OPIOID SYSTEM AND OPIOID ANALGESIC MECHANISMS

Opioid analgesics produce therapeutic and side effects by mimicking endogenous opioid activity, although some opioids produce analgesia by activity outside the opioid receptor complex. Opioids widely differ in levels of affinity and activation of opioid receptor subtypes. In addition, inter-individual variation in analgesic response and side effects is significant, largely driven by genetic factors [103]. The complex interaction between unique opioid properties and individual patient characteristics dictates that a patient-tailored approach is required for opioid selection, dose initiation, and titration to optimize safety, analgesia, and tolerability.

Naturally occurring opioid compounds are produced in plants (e.g., opium, morphine) and in the body (the endogenous opioids) [104]. Endogenous opioids are peptides that bind opioid receptors, function as neurotransmitters, and help regulate analgesia, hormone secretion, thermoregulation, and cardiovascular function. The three primary endogenous opioid peptide families are the endorphins, enkephalins, and dynorphins, and the three primary opioid receptor types are mu, kappa, and delta [105; 106]. A quick overview of this complex pain modulation system is helpful in understanding how opioid analgesics work.

ENDOGENOUS OPIOID PEPTIDES

Endogenous opioid peptides are neurotransmitter molecules in the opioid receptor complex that produce specific physiologic effects determined by neuronal distributions of the activated opioid receptor type [107]. The endogenous opioid peptides are cleaved from the pro-hormone precursors proenkephalin, pro-opiomelanocortin, and prodynorphin. The endogenous delta opioid receptor peptides are met-enkephalin and leu-enkephalin, cleaved from proenkephalin. Prodynorphin gives rise to kappa opioid receptor agonists dynorphin A

and B. Pro-opiomelancortin encodes the peptide beta-endorphin, which has agonist activity at all three classical opioid receptors. Some endogenous opioid ligands lack specificity for opioid receptor subtypes, such as b-endorphin and the enkephalins [108; 109].

Endorphins

Endorphins are synthesized in the hypothalamus and the pituitary gland. Pain, strenuous exercise, excitement, and orgasm stimulate their release, binding, and activation. Endorphins are popularized as the "natural pain killers" from their ability to induce analgesia and a general feeling of well-being. They are thought to largely mediate analgesia from acupuncture, massage, hydrotherapy, and transcutaneous electrical nerve stimulation therapy [110].

Dynorphins

Dynorphin peptides are synthesized from the precursor pro-dynorphin and have primary affinity and binding at the kappa opioid receptor. Dynorphins are distributed throughout the CNS, with highest concentrations in the brain stem, hypothalamus, and spinal cord. Their physiologic actions are diverse, and their primary function is the modulation of pain response, appetite and weight, circadian rhythm, and body temperature. Dynorphins are linked to stress-induced depression and drug-seeking behavior, and drugs that inhibit dynorphin release are under evaluation for possible use in the treatment of depression related to drug addiction [110].

Enkephalins

Enkephalin peptides, derived from pro-enkephalin, are located throughout the brain and spinal cord and are involved in regulating nociception. Enkephalins inhibit neurotransmission in pain perception pathways, reducing the emotional and physical impact of pain. Enkephalins also reside in the GI tract, where they help regulate pancreatic enzyme secretion and carbohydrate metabolism [110].

OPIOID RECEPTORS

Opioid receptors are expressed throughout the CNS and PNS on key nodes within the pain pathway and are highly concentrated in areas involved with integrating pain information [61]. Opioids vary greatly by receptor affinity, binding, and activity and can bind to produce agonist, partial agonist, or antagonist receptor activity [105]. As noted, the analgesic activity and the side effects result from mimicry of endogenous opioids, achieved by the beta-phenylethylamine group moiety shared by endogenous and exogenous opioid receptor ligands that facilitate opioid receptor binding [111].

Mu Opioid Receptors

Mu receptors are the primary mediators of analgesia produced by opioid analgesics in clinical use. Their greatest CNS concentration is in the thalamus, medulla, periaqueductal gray area, neocortex, amygdala, dorsal horn, inferior and superior colliculi, and brain stem [105; 110; 112]. PNS occupancy includes the peripheral sensory neuron dorsal root ganglion, stomach, duodenum, jejunum, ileum, and proximal and distal colon. Mu receptors in non-neural tissue are found in the vascular and cardiac epithelium, keratinocytes, vas deferens, and Sertoli cells [113].

Mu opioid receptors in the amygdala and nucleus accumbens mediate opioid reward response (e.g., euphoria). In this brain region, opioids bind to and activate mu receptors, which inhibit gamma-aminobutyric acid (GABA) to increase dopamine transmission [61]. Mu opioid receptors broadly distributed in the limbic system mediate emotional response to pain and analgesia. In the medial thalamic nuclei, they relay spinothalamic inputs from the spinal cord to the cingulate gyrus and limbic structures [114].

Kappa Opioid Receptors

Kappa opioid receptors bind dynorphin as the primary endogenous ligand. In the CNS, they are highly concentrated in the caudate-putamen, nucleus accumbens, amygdala, brain stem, neural lobe of the pituitary gland, and hypothalamus. In the PNS, these receptors are found in the sensory neuron dorsal root ganglion, stomach, duodenum, jejunum, ileum, and proximal and distal colon. They are primarily found in the limbic system, brain stem, and spinal cord. Their major effects include spinal analgesia, sedation, dyspnea and respiratory depression, dependence, and dysphoria [113]. The kappa opioid receptor subtype k3 is considered the primary analgesic mediator [49].

Delta Opioid Receptors

Delta receptors are mostly confined to CNS structures of the pontine nuclei, amygdala, olfactory bulbs, and deep cortex, but are also found in the GI tract and the lungs. They mediate spinal and supraspinal analgesia and the psychomimetic and dysphoric effects of opioid analgesics [16; 110].

Other Potential Opioid Receptors

Other opioid-like receptors have been identified in the CNS, including the opioid receptor like-1 (ORL-1). In contrast to the classic opioid receptors, the ORL-1 receptor is insensitive to the opioid antagonist naloxone. Opioids can bind to and activate the toll-like receptor 4 (TLR4), an innate immune pattern-recognition receptor [61].

OPIOID ANALGESIC MECHANISM

Opioid analgesia results from a complex series of neuronal interactions, largely mediated by the high density of opioid receptors in the dorsal horn of the spinal cord and in subcortical regions of the brain [107]. The analgesic effects of opioids result from two general processes: 1) direct inhibition of ascending transmission of pain signaling from the dorsal horn of the spinal cord, and 2) activation of descending pain control circuits from the midbrain to the dorsal horn of the spinal cord [110]. All three opioid receptor types mediate spinal analgesia. Supraspinal analgesia is primarily mediated by mu opioid receptor subtype 1. Opioid receptors are coupled to the superfamily of inhibitory G proteins. Receptor activation inhibits adenylate cyclase, reducing generation of cyclic adenosine 3,5 monophosphate and other second messengers. Potassium conduction is activated, inhibiting calcium influx to hyperpolarized target cells and reducing their response to depolarizing pulses. Neurotransmitter release is inhibited, and generation of postsynaptic impulses is decreased [61; 107].

Although drugs such as morphine are highly selective for mu opioid receptor and bind multiple mu receptor subtypes, mu opioid agonists greatly differ by interaction with different receptor variants and other opioid and non-opioid receptors [106].

Spinal Level

The spinal cord dorsal horn is a primary analgesic site of opioids and is densely populated with mu (70%), delta (20%), and kappa (10%) opioid receptors. Opioid receptors are localized on presynaptic afferent fibers, interneurons, and postsynaptic projection neurons [61]. Opioids bind to and activate mu receptors, which inhibit the release of pain mediators such as substance P, glutamate, and nitric oxide from nociceptive afferent neurons. Spinal level analgesia appears to elevate pain thresholds [107].

Supraspinal Level

At supraspinal levels, opioids produce analgesia by attenuation of the subjective evaluation of pain. After morphine is given for severe pain, patients report pain but without the associated anguish and distress. Conscious awareness and pain response are retained but modified by changes in emotional response to pain, mediated in part through opioid receptors in the limbic system [107].

Opioid receptors are highly concentrated in the medial thalamus, where incoming sensory information associated with intense and deep pain is filtered and then relayed to the cerebral cortex. This opioid effect on medial thalamus pain signal filtering greatly contributes to analgesia [107].

Opioid receptors are highly localized in subcortical brain regions where descending pain-modulating pathways originate. Normally, these pathways are inhibited by GABAergic neurons that project to descending inhibitory neurons of the brain stem. Opioid analgesics bind to and activate mu receptors on GABAergic neurons; this inhibits GABA to activate descending pain-modulating pathways [61; 107]. In addition, opioids activate ascending serotonin/norepinephrine pathways that project to forebrain centers to regulate the emotional response to pain [105].

The greatest factor that contributes to opioid analgesia is concentration of the drug on the mu receptor, which can be altered by pharmacokinetic processes that influence plasma concentration of the opioid by impacting its absorption, distribution, metabolism, or excretion. Intrinsic properties of the opioid, such as lipid solubility, also contribute to opioid receptor concentration [115].

Neuropathic Pain

Opioid analgesics have historically been considered less effective in neuropathic pain, but more recent evidence provides some support for their use. The extent of neuropathic pain reduction correlates with the duration of opioid therapy, possibly accounting for the mixed results in short-term studies [116; 117]. A 2011 study discovered previously unknown mu and kappa receptor expression on numerous peripheral tissues, immune cells, and joint capsules/synovium. The administration of opioids by injection into painful peripheral tissue sites results in pain relief in the absence of CNS activity, which supports the existence of localized peripheral opioid receptors [118].

Opioid effectiveness in neuropathic pain may be influenced by the capacity to inhibit voltage-gated sodium channels and individual channel type. Buprenorphine is more effective in blocking sodium channels than meperidine, lidocaine, and bupivacaine, possibly from greater lipophilicity, as this is a major factor in local anesthetic potency [117]. Sufentanil, fentanyl, and tramadol, but not morphine, are effective in blocking neuronal Nav 1.2 and may have greater clinical effect in some forms of neuropathic pain [119].

Inflammation enhances opioid anti-nociceptive action by peripheral mechanisms that activate during later (but not early-stage) inflammation, suggesting that timing of opioid administration contributes to analgesic efficacy in inflammatory pain [118]. Opioids are also effective in reducing the "air hunger" of dyspnea in patients suffering from cancer or respiratory or cardiovascular insufficiency [105].

OPIOID ANALGESIC PHARMACOLOGY

Opioids have been a mainstay of pain treatment for thousands of years and remain so today. The opium poppy, *Papaver somniferum*, is the oldest and most prevalent source of opium and opioid analgesics. The opium poppy was grown in the Mediterranean region at least as early as 5000 B.C.E. and has since been cultivated in a number of regions throughout the world.

The first historical medical reference to opium dates back to the 3rd century B.C.E. by Arab physicians experienced in its therapeutic uses. In 1806, Friedrich Sertürner reported the isolation of a pure substance in opium that he named morphine, after Morpheus, the Greek god of dreams [110]. Sertürner also published the first report of morphine toxicity in 1817. In this account, he discussed his experimentation of administering the

alkaloid to himself, three young boys, three dogs, and a mouse. One of the dogs died, and the effects of morphine on Sertürner and his three young volunteers were described as "near-fatal." In the 1850s, the first recorded morphine overdose fatality was reported by Alexander Wood when performing one of the first morphine injections on his wife, who subsequently died of respiratory depression [120].

Raw opium contains numerous alkaloids, but only morphine, codeine, thebaine, and papaverine have an identified use in medicine. Because the synthesis of morphine is difficult, the opium poppy plant remains the primary source of morphine [105]. Thebaine is a minor constituent of opium that chemically resembles morphine and codeine but produces a stimulant, rather than calming, effect. Thebaine is not used medicinally but is converted into oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, and buprenorphine [122].

The numerous synthetic derivatives of morphine and thebaine are produced by relatively simple modifications of the parent molecule. For example, morphine is transformed into codeine by methyl substitution on the phenolic hydroxyl group and into diacetylmorphine by acetylation at the 3 and 6 positions (to produce heroin). Structural alteration of opioid molecules has been performed with the goal of producing an opioid molecule with greater opioid receptor affinity, to alter drug activity from agonist to antagonist, to change lipid solubility, and to increase resistance to metabolic breakdown. Although numerous opioid analgesics have been developed with clinical effects similar to morphine, morphine remains the criterion standard by which the analgesic efficacy of new opioids is measured [105].

There are several ways to classify the various opioids (***Table 1***). The traditional approach to opioid classification is grouping by analgesic potency into strong, intermediate, and weak subgroups [16]. Opioids may also be grouped into chemical classes, including phenanthrenes (the prototypical opioids), benzomorphans, phenylpiperidines, diphenylheptanes, and phenylpropyl amines [104]. A more pharmacologically and clinically relevant classification approach is grouping by functional interaction as mu receptor agonists, partial agonists, mixed agonists-antagonists, or antagonists. For the purposes of this course, currently available opioids will be grouped and discussed by functional class.

Each opioid has a unique analgesic and adverse effect profile that reflects differences in opioid receptor selectivity, binding affinity, and activity (***Table 2***) [115]. Understanding the unique receptor activity profile of individual opioids can assist in the selection process. These inter-opioid differences help account for incomplete cross-tolerance, the basis for opioid rotation [173].

MU OPIOID RECEPTOR FULL AGONISTS

Mu opioid receptor agonists include the most powerful analgesics used in medicine and possess the greatest analgesic potency among opioids. Properties of opioids in this group include increasing efficacy with dose escalation, absence of a ceiling effect (defined as further dose increases failing to increase analgesia beyond a certain level), and lack of antagonism of other concurrently administered mu opioid receptor agonists. Despite these shared properties, substantial pharmacologic and clinical differences are found among these agents [16; 123].

OPIOID ANALGESIC CLASSIFICATION SCHEMES		
Category	**Example Drugs**	
Analgesic Potency		
Weak	Codeine	
Intermediate	Buprenorphine Pentazocine Butorphanol Nalbuphine	Hydrocodone Tramadol Tapentadol
Strong	Morphine Oxycodone Hydromorphone Oxymorphone	Levorphanol Fentanyl and analogs Methadone Meperidine
Chemical Class[a]		
Phenanthrenes	Morphine Codeine Hydromorphone Levorphanol Oxycodone	Hydrocodone Oxymorphone Buprenorphine Nalbuphine Butorphanol
Benzomorphans	Pentazocine	
Phenylpiperidines	Meperidine	Fentanyl and analogs
Diphenylheptanes	Methadone	
Phenylpropyl amines	Tramadol	Tapentadol
Functional Activity[b]		
Full agonist	Morphine Codeine Hydromorphone Levorphanol Oxycodone Hydrocodone	Oxymorphone Methadone Fentanyl and analogs Meperidine Tramadol Tapentadol
Partial agonist	Buprenorphine	
Mixed agonist/antagonist	Pentazocine Nalbuphine	Butorphanol
Antagonist	Naloxone Naltrexone	Alvimopan Methylnaltrexone
[a]Under each class, the first listed opioid is the prototypical agent [b]At the mu opioid receptor		
Source: [16; 104]		*Table 1*

Morphine

Morphine (Roxanol, MS Contin, Avinza, Kadian, MorphaBond, Embeda) was first isolated from raw opium in 1803 and introduced as an analgesic in the United States in 1830. Hypodermic syringes were introduced in the mid-19th century, making morphine available for parenteral use with improved analgesic, sedative, and antitussive properties [124; 125]. Morphine is the prototypical opioid and remains one of the most effective drugs for alleviating severe pain, remarkable given its clinical use spanning almost two centuries. The World Health Organization has designated morphine as a drug of choice for moderate-to-severe pain [103].

RECEPTOR BINDING AFFINITY OF OPIOID ANALGESICS						
Opioid Analgesic	Opioid Receptor			Other Receptors		
	Mu	Kappa	Delta	NE	5-HT	NMDA
Agonists						
Codeine	+		+			
Hydrocodone	+	+	+			
Morphine	+++	+	+			
Fentanyl	+++					
Hydromorphone	++		+			
Oxycodone	++	+	+			
Oxymorphone	+++					
Methadone	++		+	+	+	--
Meperidine	+	++	+			
Levorphanol	+++	+	+	+		--
Tapentadol	+			+		
Tramadol	+			+	+	
Partial agonist						
Buprenorphine	+	-				--
Agonist-antagonists						
Pentazocine	-	++				
Nalbuphine	-	+	+			
Butorphanol		+				
Antagonist						
Naltrexone	---	---	-			

+ = Low/moderate agonist
++ = Moderate/high agonist
+++ = High-affinity agonist
- = Low/moderate antagonist
-- = Moderate/high antagonist
--- = High-affinity antagonist
5-HT = serotonin, NE = norepinephrine, NMDA = *N*-methyl-D-aspartate.

Source: [16; 115; 117] *Table 2*

Morphine is a strong mu opioid receptor agonist and a weak kappa and delta receptor agonist. It can be administered intramuscularly (IM), intravenously (IV), subcutaneously (SC), rectally, epidurally, intrathecally, or orally. With IM/SC injection, the onset of effect occurs after 15 to 30 minutes, peak effect in 45 to 90 minutes, and duration of effect in roughly 4 hours. Following IV injection, the peak effect occurs in 15 to 30 minutes. When given IV, only a small portion of morphine reaches the CNS due to poor lipid solubility, a high degree of ionization at physiologic pH, protein binding, and rapid metabolism [115]. Morphine produces analgesia, euphoria, and a sensation of warmth. It increases pain threshold and alters the perception of noxious stimuli, even at low doses. Continuous, dull pain and pain originating in visceral organs, skeletal muscles, joints, and bone are most responsive to morphine [110].

The analgesic and respiratory depressant effects of morphine may not correlate with plasma concentrations, because CNS concentration peaks later and decays more slowly than plasma concentration. When given orally, morphine undergoes extensive first-pass hepatic metabolism, resulting in 40% to 50% of the oral dose reaching the CNS [115]. The elimination half-life of approximately two hours is independent of route of administration or formulation. Morphine administered by sublingual and buccal routes has a delayed onset of action compared with oral morphine (due to smaller peak plasma levels, lower bioavailability, and larger interpatient variability). Compared with the oral form, intrathecal morphine is 100 times more potent and epidural morphine is 10 times more potent (i.e., 0.5 mg intrathecally equals 5 mg epidurally) [103].

Oral morphine preparations are available in short-acting (SA) and ER formulations, including an ER formulation containing naltrexone to discourage tampering and diversion [115].

Hydromorphone

Hydromorphone (Dilaudid, Exalgo) is a semi-synthetic hydrogenated ketone of morphine with primary activity as a mu receptor agonist. It has roughly five to seven times the potency of morphine, with similar effects but possibly less sedation and greater euphoria [110]. Hydromorphone can be administered by parenteral, IV, rectal, and oral routes and is considered the best opioid for SC administration. Oral hydromorphone has a bioavailability of 50% and plasma elimination half-life of 2.5 hours [103]. Its high water solubility permits very concentrated formulations. A meta-analysis found significantly better analgesia with hydromorphone than morphine for acute pain, without significant differences in adverse effects [126].

Following oral administration of conventional-release hydromorphone, the drug is rapidly absorbed and undergoes hepatic first-pass elimination of approximately 50%. The terminal elimination half-life after IV administration is 2.5 to 3 hours, and the primary mode of elimination is through urinary elimination in the form of hydromorphone-3-glucuronide, the primary metabolite. Some metabolites may have greater analgesic activity than hydromorphone itself but probably do not contribute to its pharmacologic activity. The side effects are similar to morphine [127].

The first ER formulation of hydromorphone (Palladone) was approved for marketing in 2004. However, at the request of the FDA, Palladone was withdrawn from the U.S. market in 2005 by its manufacturer, Purdue Pharma, over the potentially fatal interaction with alcohol [128]. Another ER formulation, Exalgo, has since been introduced without this liability [129].

Codeine

Codeine (Tylenol with Codeine, Capital with Codeine, Vopac) produces analgesia solely through enzymatic conversion into morphine, so it is considered a pro-drug. A pro-drug is a drug ingested in a biologically inactive (or less active) form and biotransformed into an active (or more active) metabolite [130].

The oral bioavailability of codeine is 50%, with roughly 10% metabolized to morphine. However, at least 10% of individuals possess deficient activity of the hepatic enzyme necessary to metabolize codeine to morphine due to genetic variation or polymorphism. In these individuals, codeine has no analgesic effect and should be avoided.

Codeine can be used orally or IM for mild-to-moderate pain but has very limited use in severe pain. Codeine is also used as an antitussive and antidiarrheal. Codeine produces minimal euphoria, has low abuse liability, is less sedating, and is less likely to result in respiratory depression than morphine. Constipation is a common side effect. Because commercially available codeine is combined with acetaminophen or acetylsalicylic acid (ASA), the dosage should be monitored to ensure daily safe limits are not surpassed [104]. Codeine has an analgesic ceiling, with no additional analgesic benefit from doses greater than 60 mg [131].

Oxycodone

Oxycodone (Oxy IR, Percocet, Tylox, OxyContin, Xtampza ER, Targiniq ER) is a semisynthetic opioid analgesic derived from the natural alkaloid thebaine and has been in medical use since 1917. Although oxycodone mu opioid receptor affinity is at least 20 times less than morphine, oxycodone possesses high oral bioavailability and delivers analgesia and other subjective effects comparable to oral morphine [103]. Unlike morphine, oxycodone has moderate affinity and agonist activity at the kappa-2b opioid receptor, which contributes to its efficacy in neuropathic pain [117].

Oxycodone is available in SA and ER oral formulations. Oxycodone SA has a half-life of approximately two to four hours and a bioavailability of 50% to 60%. The overall clinical effects of oxycodone reflect primary mu receptor activity, with analgesia, respiratory depression, euphoria, and abuse liability comparable to other mu agonists. Oxycodone differs from morphine by producing less dysphoria and by more rapid transport through the blood-brain barrier, resulting in greater CNS than plasma concentrations, the reverse of morphine [117].

In addition to its low-dose combination with acetaminophen, oxycodone is formulated as the sole analgesic in 10-, 20-, 40-, and 80-mg controlled-release (CR) tablets and 5-mg SA capsules. Sales of oxycodone CR (OxyContin) 160 mg were discontinued by Purdue Pharma in 2001 over abuse and diversion concerns [132].

Oxymorphone

Oxymorphone (Numorphan, Opana) was first synthesized in Germany in 1914, patented in the United States in 1955, and introduced in 1959 for parenteral injection and in suppository form. It then became available as an oral SA opioid, but this was withdrawn from the U.S. market in the early 1970s. Following reintroduction in 2006 in oral SA and ER formulations, its use in the treatment of noncancer pain has steadily increased [133].

Oxymorphone is a semisynthetic derivative of the parent compound morphine and has a high affinity for the mu opioid receptor and negligible interaction with kappa and delta opioid receptors [134]. The potency is roughly 1.2 times that of morphine, but with less sedative effects [16]. Oxymorphone possesses less protein binding (10% to 12%) than morphine (30% to 35%) and oxycodone (45%), and its highly lipophilic properties provide ease in blood-brain barrier penetration [129]. The oral bioavailability of oxymorphone is approximately 10%, the lowest of the full agonists. In healthy volunteers, the half-life ranges from 7.2 to 9.4 hours, longer than that of morphine, hydromorphone, and oxycodone. Oxymorphone SA tablets may be given at six-hour intervals, whereas the ER formulation is dosed twice daily. Steady-state conditions are achieved after three to four days. Oxymorphone is subject to hepatic first-pass effects and is excreted by the kidneys. As such, this agent has a prolonged half-life and accumulates in patients with renal failure. In patients with hepatic insufficiency, increasing the dosing interval is recommended [103].

Oxymorphone is an effective opioid analgesic with a safety profile comparable to other mu agonist opioids. It may have a safety advantage in elderly or frail patients for whom adverse drug interactions are concerning [135]. However, in 2017, the FDA requested Opana ER be removed from the market amid abuse concerns [267].

Hydrocodone

Hydrocodone (Zohydro ER, Hysingla ER, Lortab, Vicodin) is a semi-synthetic codeine derivative that more closely resembles morphine in its pharmacologic profile. Hydrocodone was first used medically as a cough suppressant and analgesic in the 1920s [122; 136]. It exhibits a complex pattern of metabolism, including demethylation at the 3-carbon position into hydromorphone, which has stronger mu receptor binding than the parent drug. Thus, similar to codeine, hydrocodone is suggested to be a pro-drug. Its analgesic properties are similar in potency to codeine [16].

Hydrocodone is effective as a cough suppressant and as an analgesic for moderate to moderately severe pain. It is most frequently prescribed in combined formulations with acetaminophen (Vicodin, Lortab), aspirin (Lortab ASA), ibuprofen (Vicoprofen), and antihistamines (Hycomine) and as an antitussive liquid formulation [122]. The hydrocodone/ibuprofen product is intended for short-term (generally less than 10 days) management of acute pain from trauma, musculoskeletal or back pain, postoperative pain, abdominal pain, or dental pain. Two single-entity hydrocodone ER products are now available; in addition to sparing patients with comorbidity or who require long-term use from acetaminophen or nonsteroidal anti-inflammatory drug (NSAID)-related adverse effects, these products are thought to provide more stable analgesic with slow release and less euphoria [137].

Methadone

Methadone (Dolophine, Methadose) was first synthesized as an analgesic in Germany during World War II in response to the difficulty obtaining raw opium to synthesize morphine [138]. Although chemically unlike morphine or heroin, methadone produces many of the same pharmacologic and clinical effects. It was introduced into the United States in 1947 as the analgesic Dolophine.

High-dose methadone can block the effects of heroin and other opioid drugs by diminishing reward and reinforcement effects, and this has been the primary use of methadone in the United States over the last five decades. In the late 1990s, methadone entered clinical use as an analgesic [122].

Methadone is available in racemic form with a 50:50 mixture of two enantiomers: a levo-(R)-enantiomer and a dextro-(S)-enantiomer. The 1(R)-enantiomer produces opioid analgesia as a mu opioid receptor agonist, while the d(S)-enantiomer functions as an *N*-methyl-D-aspartate (NMDA) receptor antagonist and reuptake inhibitor of serotonin and norepinephrine. These pharmacologic properties expand indications for its use beyond those of most other mu receptor agonists [117]. Methadone produces analgesia very similar to other commonly used opioids, but its lack of euphoric effects relative to other agents can make it advantageous in some patient populations. NMDA receptor antagonism can make methadone highly beneficial in managing patients with a history of prolonged opioid use with high opioid tolerance or opioid-induced hyperalgesia [110].

In the inpatient setting, IV methadone can be very effective in managing patients with true morphine allergies. Patients predicted to have long-term opioid requirement can initiate with IV methadone and are easily transitioned to oral methadone [110]. The highly variable elimination half-life is 8 to 60 hours, and single-dose analgesia lasts 4 to 8 hours. This necessitates great caution during initiation and titration, because patients may re-dose when analgesia wears off and pain reappears, leading to accumulation, toxicity, and overdose [110]. Methadone requires a thorough understanding of its pharmacokinetic properties to safely prescribe.

The American Society of Interventional Pain Physicians recommends methadone for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed May 13, 2020.)

Level of Evidence: I (Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness)

Levorphanol

Levorphanol is the only commercially available opioid agonist of the morphinan series and the levo-enantiomer of dextrorphan, a potent NMDA receptor antagonist [139]. Levorphanol was first synthesized more than 40 years ago as an alternative to morphine, and it produces effects very similar to morphine, with greater potency. Analgesia is produced by activity as a mu, delta, and kappa opioid receptor agonist, NMDA receptor antagonist, and norepinephrine and serotonin reuptake inhibitor. The NMDA receptor antagonist potency of levorphanol is equivalent to ketamine and superior to methadone [49]. Single-dose analgesic duration is 6 to 8 hours, and the elimination half-life is 11 hours. This increases the potential for drug accumulation, and patients should be observed for toxicity during the initial two to five days. Roughly 50% of oral levorphanol clears first-pass metabolism and is bioavailable [140]. Initiate dosing every four hours, and every six to eight hours when steady state is reached (after one to two weeks) [15; 140].

During the 1980s, levorphanol fell into disuse with the introduction and aggressive marketing of ER forms of morphine, oxycodone, and fentanyl. Renewed interest in this drug was prompted by recognition that many patients with neuropathic pain do not obtain pain control with standard full-agonist opioids. Levorphanol shows promise in treating neuropathic pain, severe pain in hospice patients, and severe pain in patients with chronic noncancer pain uncontrolled by other mu opioid receptor agonists. With empirical confirmation, levorphanol has potential as first-line or second-line therapy for these indications, but little research has been published on this drug [46; 49; 140; 141].

The brand-name drug Levo-Dromoran is discontinued, and no parenteral form is available. The sole available dose and formulation for levorphanol is an oral 2-mg tablet [140]. As a generic drug, levorphanol has not been promoted or marketed [141].

Roxane Pharmaceuticals stopped manufacturing levorphanol in 2015. Shortly thereafter, Sentynl Therapeutics, Inc., released a "new" levorphanol to the market. Unfortunately for pain sufferers who responded well to levorphanol, the average wholesale price of 2-mg tablets increased 2,073%, from $214/100 tablets to $4,650/100 tablets [142].

Fentanyl and Analogs

Fentanyl (Duragesic) is a phenylpiperidine-class opioid and is structurally similar to meperidine. Fentanyl was first synthesized in Belgium in the late 1950s and introduced to the U.S. market in the 1960s as an IV anesthetic. Other fentanyl analogues were subsequently introduced, including alfentanil, an ultra-short acting (5 to 10 minutes) analgesic; sufentanil, an exceptionally potent analgesic (1,000 times more potent than morphine) for use in cardiac surgery; and remifentanil, with similar potency to fentanyl and ultra-short duration of 3 to 10 minutes [105].

Fentanyl has an analgesic potency 80 to 100 times that of morphine. The highly lipophilic nature of the molecule allows rapid blood-brain barrier penetration and quick onset of action (two to three minutes with IV administration). Primary clinical effect comes from mu receptor agonist activity and to a lesser extent from kappa and delta receptor activity [143]. The pharmacologic profiles of fentanyl and its congeners (sufentanil, remifentanil, and alfentanil) are similar to other mu-receptor agonists, although fentanyl produces fewer side effects of sedation, nausea and vomiting, urinary retention, and pruritus than morphine or hydromorphone [110]. The fentanyls are distinguished from other mu opioid receptor agonists by shorter time to peak analgesic effect, rapid termination of effect after small doses, and relative cardiovascular stability, making them very popular for surgical use.

The respiratory depression potential is similar to other mu receptor agonists, with a more rapid onset [105]. Fentanyl formulations include several transmucosal and buccal preparations for rapid-onset analgesia in breakthrough pain, and a transdermal preparation for sustained analgesia in chronic pain.

Transmucosal immediate-release fentanyl formulations are approved by the FDA for use in breakthrough pain. Transdermal fentanyl was developed to circumvent unsuitability for oral use and is indicated for continuous sustained-release analgesia in the treatment of chronic pain [144]. With initial use, the 6- to 12-hour lag time from application to onset of action requires the use of short-acting opioids for analgesic coverage and for breakthrough pain; morphine, tapentadol, or oxycodone are preferred. Steady state is usually achieved in three to six days. With patch removal, a subcutaneous reservoir remains, and up to 24 hours is usually needed for drug clearance [16; 115].

Tramadol

Research efforts into mechanisms of pain relief during the 1990s focused on centrally mediated monoamine transmission and its influence on chronic and neuropathic pain. Clinical evidence demonstrated that increasing the extracellular concentrations of serotonin and norepinephrine in descending pain inhibitory pathways produced an analgesic effect. Norepinephrine is the primary monoamine contributor to pain signal attenuation and is especially useful in neuropathic pain. Combining an opioid agonist with a monoamine reuptake inhibitor was hypothesized to produce opioid-sparing effects, increased pain control, and decreased adverse effects. These efforts led to the development of tramadol and tapentadol [49].

Tramadol (Ultram, ConZip) is a synthetic codeine analog from the aminocyclohexanol structural group and a racemic compound. The positive enantiomer acts as a serotonin reuptake inhibitor, with 30% of total analgesic effect from weak mu opioid receptor agonism; the negative enantiomer inhibits norepinephrine reuptake [117]. Tramadol has greater efficacy in neuropathic than nociceptive pain. Monoamine reuptake inhibition accounts for tramadol's efficacy in neuropathic pain [117].

The primary metabolite, *O*-desmethyltramadol, has higher mu opioid receptor affinity and two to four times greater analgesic potency than the parent drug. Tramadol is as effective as morphine in mild-moderate pain. Its bioavailability is 68% following an oral dose and 100% following IM administration [145].

Tramadol has lower abuse potential than other opioids but is associated with the significant adverse drug reactions of serotonin syndrome and seizures. Dosage should not exceed 400 mg/day due to the seizure risk, and even doses less than 400 mg/day can increase seizure potential in patients with epilepsy or risk factors for seizure [117]. Seizure risk is elevated by concurrent use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), cyclobenzaprine and other tricyclic compounds, other opioids, neuroleptics, and certain other drugs. Tramadol should not be used within 14 days of monoamine oxidase inhibitors (MAOIs), as this increases risk of seizures or serotonin syndrome [16].

Tapentadol

Tapentadol (Nucynta) is a novel synthetic opioid structurally related to tramadol that was approved in 2009. It was intentionally designed to overcome the barriers to efficacy associated with tramadol, such as the potential risk for serotonin syndrome [49]. Tapentadol has 18 times less affinity for mu opioid receptor than morphine and is 5 times less potent than oxycodone (i.e., 50 mg tapentadol is equivalent to 10 mg oxycodone) [146; 147]. Tapentadol has an oral bioavailability of 32%, and plasma protein binding is 20%. Time to maximum serum concentration is achieved in 1.25 to 1.5 hours, and the half-life is 24 hours [103].

Tapentadol has no active metabolites and primarily undergoes hepatic metabolism via phase II conjugation. Tapentadol selectively inhibits norepinephrine reuptake with affinity and potency comparable to venlafaxine, which increases efficacy and avoids the potential risk for serotonin syndrome. In a study of patients with chronic pain receiving tapentadol for up to two years, 88% did not experience opioid withdrawal symptoms on abrupt withdrawal and symptoms were mild-to-moderate among those who did [148].

Analgesic tolerance develops at significantly lower rates with tapentadol than with morphine. It has a low risk for drug interactions, does not depend on metabolic activation for efficacy, and shows a lower incidence in adverse GI effects such as nausea, vomiting, and constipation relative to other opioids [49; 149].

A review of prolonged-release (PR) tapentadol concluded its broad analgesic efficacy, ease of initiating and titrating in opioid-naïve and opioid-experienced patients, favorable pharmacokinetic profile with few medication interactions, low abuse potential, and low risk of withdrawal after cessation may offer significant advantages over classic opioid analgesics. Tapentadol is not recommended in patients with severe renal or hepatic impairment, because studies are lacking in these patient populations [150].

Meperidine

Meperidine (Demerol, Meperitab) is a synthetic phenylpiperidine derivative with weak mu and kappa receptor agonist activity. It has roughly one-tenth the potency of morphine. The structural similarity to atropine is consistent with its original development as an anti-muscarinic agent. The effects are similar, but not identical, to morphine, with shorter analgesic duration and less antitussive and antidiarrheal efficacy. In equivalent analgesic doses, meperidine produces comparable sedation and respiratory depression and possibly greater euphoria than morphine, although some patients experience dysphoria. Pharmacologic differences from morphine include increased risk for tachycardia and dry mouth and less biliary tract spasm and miosis. Meperidine may significantly decrease blood pressure, especially when administered to elderly or hypovolemic patients [104; 123].

The short analgesic duration (2.5 to 3.5 hours) makes meperidine impractical for persistent pain, although it is a useful analgesic in labor and delivery and uniquely effective in treating post-operative shivering. Accumulation of the neurotoxic metabolite normeperidine contraindicates its use for longer than 48 hours or at doses of 600 mg or greater over 24 hours in any context. Normeperidine accumulation is especially likely in patients with impaired renal function. The neuroexcitatory properties of this metabolite can cause tremors, muscle twitches, delirium, or seizures; multifocal myoclonus develops before seizures and can serve as a warning sign. Normeperidine toxicity is not reversible with naloxone. Administration of meperidine to patients receiving MAOIs can lead to profound and possibly fatal autonomic instability [16; 110; 123]. Clinical use of meperidine has declined into virtual disuse in recent years [115].

Propoxyphene

Propoxyphene (Darvon, Darvocet) was first marketed in 1957 to treat mild-to-moderate pain. Propoxyphene primarily binds to mu opioid receptors to produce mild analgesia, with potency one-half to one-third that of codeine [16]. Propoxyphene also became a popular drug of abuse. In 2010, the FDA requested the removal of propoxyphene from the U.S. market due to new data showing increased risk for serious abnormal heart rhythms with its use, even at therapeutic doses [151]. This drug is no longer available domestically.

Levo-Alpha-Acetylmethadol

Levo-alpha-acetylmethadol (LAAM) is a synthetic mu opioid receptor agonist closely related to methadone, but with a longer duration of action (48 to 72 hours). LAAM was originally developed by German chemists in 1948 and as early as 1952 was identified as an agent that could prevent opioid withdrawal symptoms for more than 72 hours. In 1993, the FDA approved LAAM for the treatment of opioid addiction, with the intent to build on the strengths and improve on the drawbacks of methadone [122; 152]. However, concerns over cardiovascular toxicity and subsequent underutilization led to its withdrawal from the market in 2004 by the manufacturer, and LAAM is no longer commercially available in the United States [138].

PARTIAL AGONIST OPIOIDS

Partial agonists possess mu opioid receptor binding and activity, but to a lesser extent than full agonists such as morphine. Buprenorphine is the only commercially available partial agonist in the United States.

Buprenorphine

Buprenorphine (Belbuca, Suboxone, Subutex, Butrans) is a semi-synthetic opioid first derived from thebaine in 1966, initially as an alternative to methadone therapy for heroin addiction [153]. Injectable buprenorphine (Buprenex) was approved in 1981 for acute pain, and two sublingual formulations (Suboxone and Subutex) were approved for treating opioid addiction in 2002 [49]. The buprenorphine transdermal system was approved by the FDA in 2010 for the management of moderate-to-severe chronic pain in patients requiring continuous opioid analgesia for an extended time period. More recently, buprenorphine buccal film (Belbuca) was approved for the same indication. The transdermal and buccal products were developed to overcome the very low oral bioavailability resulting from substantial first-pass intestinal and hepatic metabolism [117].

The mu opioid receptor-binding kinetics of buprenorphine are unique. Receptor affinity is high, but buprenorphine associates and dissociates slowly (30 and 166 minutes, respectively) and incompletely (50%). This receptor saturation is particularly important with buprenorphine, because its high affinity and robust binding capacity make displacement by naloxone difficult or impossible. The relative resistance to naloxone antagonism requires higher doses for successful reversal [49].

The analgesic properties of buprenorphine mostly originate from mu opioid receptor interaction with high binding affinity and low efficacy, yielding partial agonist effects. Other contribution comes from activity as a nociceptin opioid peptide receptor partial/full agonist and kappa opioid receptor antagonist [117]. Prolonged analgesia can be achieved with buprenorphine from its highly lipophilic properties and prolonged receptor occupancy. It may have superior efficacy in neuropathic pain due to its pharmacologic profile and has also shown anti-hyperalgesic effects [117; 145]. A high-dose (15 mg) analgesic ceiling effect can occur, but this dose level is infrequent with analgesic use [122; 145]. Buprenorphine may act as a mu opioid receptor antagonist at high doses [117].

After application of the transdermal patch, plasma concentrations steadily increase, and the minimum effective analgesic dose is reached more rapidly with higher-dose patches. Steady state is reached after the third consecutive application. Bioavailability of the transdermal formulation is 60% compared with the IV route. Effective plasma levels occur within 12 to 24 hours and last for 72 hours. It takes 60 hours to reach maximum concentration. After patch removal, concentrations decrease by 50% in 12 hours, and then decline more gradually [103]. Transdermal buprenorphine has a maximum dose limited to 20 mcg per hour due to the potential for prolonged QTc wave interval at higher doses [16; 123].

Buprenorphine possesses a dose-ceiling effect for respiratory depression, reducing the likelihood of this potentially fatal consequence. Importantly, this applies only in the absence of co-ingested CNS or respiratory depressants. Side effects are similar to other opioids, but it is important to remember that as a result of its antagonist properties, buprenorphine can precipitate withdrawal symptoms in patients who are physically dependent on other commonly used opioids [110].

MIXED AGONIST/ ANTAGONIST OPIOIDS

For more than 70 years, the ultimate goal of analgesic research has been the discovery of an opioid agent producing effective analgesia without respiratory depression or abuse/addiction potential [154]. Earlier efforts in this quest led to synthesis of the first mixed agonist-antagonist, *N*-allylmorphine (nalorphine), in 1942. Although nalorphine was a potent analgesic and antagonist to most morphine effects, dosing sufficient for analgesia produced severe psychotomimetic effects that made the drug unsuitable for clinical use. However, discovery and development of this opioid lay the groundwork for subsequent synthesis of several mixed agonist-antagonists that have entered clinical use [16; 155].

Available mixed agonist-antagonists act as mu receptor antagonists and kappa receptor agonists. Those in current clinical use share the characteristics of an analgesic ceiling effect, whereby dose escalation beyond a certain point will not increase analgesia but increases side effects. These agents have a greater likelihood of the side effects of dysphoria, delusions, and hallucinations than full mu agonists and an increased risk of triggering an opioid withdrawal crisis in patients with physiologic dependence to full mu agonists. Kappa receptor agonist activity contributes to the analgesic and side effect profile.

These drugs should be used with caution in any patient currently receiving opioid agonists [16; 115; 123]. Practice guidelines recommend against using mixed agonists/antagonists in cancer pain, and their absence from practice guidelines for chronic noncancer pain reflects discouragement for use in these patients as well [15; 156; 157]. However, several niche indications for pain have emerged.

Pentazocine

Pentazocine (Talwin) was the first opioid in this class to enter clinical use following the development of nalorphine; it was introduced to the U.S. market as an analgesic in 1967 [122]. Kappa opioid receptor activation accounts for the analgesic effects and potential side effects of dysphoria and psychotomimesis [125]. The analgesic potency is 25% to 50% of morphine. Moderate analgesia is produced by an oral dose of 50 mg; with doses greater than 70 mg, an analgesic and respiratory depression ceiling occurs. Pentazocine has lower abuse potential than morphine, but prolonged daily use can lead to physical dependence. Dysphoric and psychotic side effects are dose proportional and reversed with naloxone. Pentazocine can increase serum catecholamine levels. Clinical use is restricted by limited analgesia, antagonism of concurrent mu agonist opioids, and the potential for GI and cardiovascular adverse effects [155].

Butorphanol

Butorphanol (Stadol) is a morphinan congener with a pharmacologic profile similar to pentazocine. It is more suitable for acute than chronic pain. Side effects of drowsiness, weakness, sweating, sensation of floating, nausea, and psychotic-like effects are less frequent than with pentazocine. Physical dependence can develop from regular use [105]. Butorphanol was initially available as an injectable formulation (Stadol). More recently, a nasal spray (Stadol NS) became available, and the ensuing abuse and diversion of this product led to its designation as a Schedule IV controlled substance [122].

Butorphanol is a mu opioid receptor antagonist and kappa opioid receptor agonist, and the opioid receptor affinity ratio of 1:25:4 for mu, kappa, and delta receptors, respectively, indicates greater delta than mu opioid receptor affinity [158]. With parenteral administration, butorphanol has analgesic potency five to eight times greater than morphine. It has a rapid onset, with peak analgesia within 1 hour, plasma half-life of 2 to 3 hours, and elimination half-life of 4.5 to 5 hours. With oral administration, bioavailability is 17% that of a comparable IV dose. The intranasal formulation is commonly used in the treatment of migraine headache. The IV formulation is effective in moderate-to-severe pain and is typically used for postoperative pain and pain control during labor. With analgesia mediated by kappa and not mu receptor activation, butorphanol may be an effective analgesic option in patients with history of opioid use disorder [110]. At a dose of 10 mg IM, butorphanol induces respiratory depression similar to a comparable morphine dose, but the level of depression does not increase with dose escalation due to the ceiling effect [159; 160].

Nalbuphine

Nalbuphine (Nubain) is similar in structure to naloxone, with primary activity as a kappa opioid receptor agonist, a mu opioid receptor partial antagonist, and delta receptor activity. On a per-milligram basis, analgesic potency is comparable to morphine, and opioid antagonist potency is one-fourth that of nalorphine and 10 times that of pentazocine. Respiratory depression is similar to morphine at equianalgesic doses, does not increase at doses greater than 30 mg, and is reversed by naloxone. With IV administration, onset is 5 to 10 minutes, duration is 3 to 6 hours, and elimination half-life is roughly 5 hours.

The most common side effect is sedation. Nalbuphine produces less dysphoria than other mixed agonist-antagonists and may produce euphoria; hemodynamic parameters are unaffected. Nalbuphine can reverse the respiratory depression and pruritus produced by mu agonists while maintaining analgesia; in this context, it is co-administered epidurally [110; 161; 162; 163].

OPIOID ANTAGONISTS

A fourth group of opioids, opioid antagonists, bind and inactivate opioid receptors. Naltrexone and naloxone have traditionally been used to reverse potentially fatal overdose from opioid receptor agonists such as morphine or heroin. Opioid agonist molecules on mu opioid receptor are displaced, agonist effects on mu opioid receptor are abruptly halted, and opioid-dependent patients rapidly experience full alertness, analgesic loss, and opioid withdrawal [164].

Clinical trials with low-dose naltrexone have found unexpected and paradoxical enhancement rather than blockade of analgesia when co-administered with morphine and other opioid agonists in postoperative pain or severe intractable pain. Other evidence suggests analgesic efficacy as monotherapy in Crohn disease, irritable bowel syndrome, and fibromyalgia [165]. These findings led to the development and introduction of the peripheral-acting mu receptor antagonists alvimopan, methylnaltrexone, and naloxegol for severe opioid-induced constipation [166; 167].

In addition to opioid-induced constipation, opioid antagonists are FDA-approved for the treatment of alcohol and opioid use disorder (naltrexone 50–100 mg/day oral) and opioid overdose (naloxone 0.4–1.0 mg/dose IV or IM). In pain medicine, the dose ranges of naltrexone and naloxone are substantially lower. Of the two, naltrexone is much more widely used, and published pain medicine studies have used dose ranges of 1–5 mg (termed "low-dose") or <1 mg in microgram amounts (termed "ultra-low-dose") [165]. For example, case studies have reported dramatic improvement in refractory pain with intrathecal administration of an opioid agonist combined with ultra-low-dose naloxone in the low nanogram range [168].

The mechanism of low-dose and ultra-low-dose opioid antagonists is not fully known and is the subject of investigation [165]. One explanation describes a sequential action, whereby binding and inhibition first occurs at excitatory receptors, followed by binding at inhibitory receptors. This decrease in excitation facilitates a broader clinical expression of inhibitory function, which potentiates analgesia and reduces adverse effects. For example, with opioid-induced hyperalgesia, ultra-low-dose naltrexone appears to act through excitatory blockade to promote analgesia and tolerability [169; 170].

Naloxone

Naloxone (Narcan) is an allyl-derivative of noroxymorphone first synthesized in 1960. It acts as a competitive antagonist with slightly higher affinity for mu receptors over kappa and delta receptors, and inhibits the entire range of pharmacologic effects produced by mu agonists. Naloxone is efficiently absorbed after oral administration, but extensive hepatic first-pass metabolism (>95%) and low bioavailability makes it unsuitable for oral use [120; 125]. Following IV or IM administration, peak plasma concentration occurs at 10 minutes, the duration of action is 1 to 4 hours, and the half-life is 30 to 81 minutes [165]. Peak effect is noted in 30 minutes following intranasal administration, with a half-life of approximately two hours.

Naltrexone

Naltrexone (ReVia, Depade) has activity comparable to naloxone but with a longer duration of action and higher oral bioavailability (40%) [125]. Following oral administration of naltrexone, the peak plasma concentration occurs at 1 to 2 hours, the duration of action is up to 24 hours, and the half-life is up to 14 hours [165].

Methylnaltrexone

Methylnaltrexone bromide (Relistor) is a naltrexone derivative with high peripheral opioid receptor selectivity resulting from low lipid solubility and poor blood-brain barrier penetration into the CNS. Methylnaltrexone is indicated for opioid-induced constipation refractory to conventional therapies in patients with advanced illness receiving palliative care. It binds and antagonizes mu opioid receptors in the GI tract. With little oral bioavailability, methylnaltrexone is administered by subcutaneous injection [171].

Alvimopan

Alvimopan (Entereg) is a mu opioid receptor antagonist with limited CNS penetration due to its large molecular weight and polarity that facilitates selective GI mu opioid receptor antagonist activity. Alvimopan was developed to address the problem of bowel dysfunction following intestinal surgery and opioid use for postoperative pain. It is FDA-approved only to accelerate the time to upper and lower GI recovery after partial large or small bowel resection surgery with primary anastomosis [171]. Concerns over the risk of serious adverse cardiovascular events led the FDA in 2012 to restrict its use to a maximum of 15 capsules, a seven-day maximum duration, used only in hospitalized patients and only in hospitals with documented registration and completion of the Entereg Access Support and Education (EASE) program, a risk management program specific to alvimopan [172].

Naloxegol

Naloxegol (Movantik) is a polymer conjugate of naloxone administered orally once daily. It is FDA-approved for the treatment of opioid-induced constipation in adults with chronic noncancer pain. The 25-mg dose appears similar in efficacy to the 12.5-mg dose, with greater side effects associated with the higher dose. In phase III trials, the most common side effects were abdominal pain (21%), diarrhea (9%), nausea (8%), flatulence (6%), vomiting (5%), headache (4%), and hyperhidrosis (3%) [171].

OTHER OPIOIDS IN CLINICAL USE

Diphenoxylate (Lomotil) and loperamide (Imodium) are meperidine congeners FDA-approved for the treatment of diarrhea. Both drugs bind intestinal opioid receptors to slow GI motility through action on intestinal circular and longitudinal muscles. At approved anti-diarrheal doses, both agents lack significant CNS effects [105].

PHARMACOKINETIC FACTORS IN OPIOID ANALGESIC RESPONSE

Pharmacokinetics is the process by which the body absorbs, distributes, metabolizes, and excretes a drug, and pharmacokinetic factors fundamentally influence the safety, efficacy, and tolerability of opioid analgesics. This is true with fatal toxicity, whereby rising serum opioid concentrations overwhelm a patient's physiologic capacity to clear the opioids through metabolism and elimination. Aside from high-dose ingestion, fatal and nonfatal toxicity results from interference with opioid metabolism and excretion from genetic factors, drug interactions, medical comorbidities, or opioid analgesic formulation and dosing. These risks can be mitigated by improved prescriber knowledge and skills.

ABSORPTION AND DISTRIBUTION

Most opioids, including morphine, oxycodone, hydromorphone, methadone, tramadol, tapentadol, fentanyl, sufentanil, buprenorphine, and codeine, possess high GI permeability and are completely absorbed from the GI tract following oral administration. However, fentanyl and buprenorphine, due to extensive hepatic first-pass metabolism, have very low oral bioavailability, rendering their oral use ineffective [1]. (This differs from sublingual and buccal administration.)

To produce analgesic action in the CNS after absorption, opioids must penetrate the blood-brain barrier; highly lipophilic opioids possess a more rapid onset due to greater ease of blood-brain barrier transport [1]. The basis for the widely variable duration of effect among opioids is complex, not always explainable by the rate of plasma clearance and terminal half-life. For example, at equivalent analgesic doses, morphine produces longer analgesia than fentanyl but has a shorter half-life. This may be explained by morphine's relatively low lipid solubility and slower diffusion out of CNS tissue [104].

METABOLISM AND ELIMINATION

Many drugs, including opioids, must undergo biotransformation to be readily eliminated from the body. Opioid analgesic molecules that produce CNS effects must be lipophilic to cross cell membranes in the blood-brain barrier, and metabolism is performed to convert lipophilic opioids into hydrophilic metabolic products for elimination. This is achieved through hepatic enzymes. The metabolic process ends when the opioid byproducts are sufficiently hydrophilic for urinary excretion [174]. Medications can be substrates at multiple cytochrome (CYP) isoenzymes, inducing one while inhibiting another.

Hepatic enzymes facilitate two forms of metabolism: phase I and phase II [174]. Phase I metabolism consists of modification of the drug molecular structure through chemical reactions such as oxidation, reduction, or hydrolysis. The predominant catalysts for phase I drug metabolism are found in the CYP450 enzymatic superfamily [130]. Phase I metabolism of some opioids produces active analgesic metabolites, as with conversions of codeine into morphine, hydrocodone into hydromorphone, and tramadol into *O*-desmethyltramadol [175]. The CYP system is comprised of more than 50 isoenzymes, but more than 90% of opioid metabolism involves the 3A4, 2D6, or 2C9 isoenzymes [145].

Phase II metabolism is a chemical reaction whereby a drug is conjugated with a chemical moiety (e.g., a glucuronide) to readily promote renal excretion. The most important Phase II conjugation reaction is glucuronidation, catalyzed by members of the uridine diphosphate glucuronosyltransferase (UGT) enzyme family. Within the UGT enzyme family, the most abundant enzyme involved in phase II opioid metabolism is UGT2B7. In most cases, the conjugated drug is rendered inactive and loses biologic activity. The exception is morphine; its conjugated metabolite, morphine-6-glucuronide, is analgesic. UGT2B7 is the primary enzyme that metabolizes morphine, hydromorphone, and oxymorphone [130].

Some opioids undergo both phase I and phase II metabolism; the breakdown products of both phases can be active or inactive. The process of metabolism ends when the molecule is sufficiently hydrophilic for efficient excretion [174].

The metabolic products of opioids differ in pharmacologic and clinical relevance. Some have analgesic activity, some are toxic with accumulation, and others are inactive. Active metabolites can bind to and activate opioid or other receptors, compete with co-administered drugs or their metabolites when metabolism involves a common pathway, or alter the activity of its CYP450 metabolic pathway.

ADVERSE DRUG INTERACTIONS

One challenge in safe opioid analgesic prescribing is avoiding adverse drug interactions. Opioids have a narrow therapeutic index, potentially fatal concentration-dependent toxicity, and wide inter-individual variability. As discussed, many fatalities associated with opioid prescribing involve at least one other offending drug, and numerous reports of fatal pharmacokinetic adverse drug interactions with opioids have been published [130]. Elderly patients and patients with medical comorbidities typically require multiple medications, termed polypharmacy, which increases the risk of adverse drug interactions. Understanding the underlying cause of these interactions can mitigate a major toxicity risk when prescribing opioids [144].

Factors that interfere with opioid metabolism or excretion can cause opioids or metabolites to accumulate (leading to toxicity) or can accelerate their elimination (leading to analgesic failure). Conditions that can lead to delayed opioid metabolism include genetic predisposition (CYP450 isoenzyme polymorphism), hepatic and/or renal dysfunction, and drug-drug interactions [164]. Adverse opioid-drug interactions can involve pharmacokinetic or pharmacodynamic interactions, and while pharmacokinetic interactions involving CYP isoenzymes (phase I) are well characterized, those involving the UGT enzyme family (phase II) are less understood.

Among opioid analgesics, CYP metabolism occurs by either the CYP206 or CYP3A4 pathway. The propensity for drug interactions is higher for opioids metabolized by CYP3A4, and this is the pathway by which most opioids in general use are metabolized [103; 130; 174]. Thus, drugs and other compounds that inhibit or induce CYP3A4 activity contribute to opioid adverse drug interactions. CYP3A4 inducers include rifampin, St. John's wort, troglitazone, and phenytoin; inhibitors include telithromycin, itraconazole, ketoconazole, miconazole, voriconazole, ritonavir, lopinavir, erythromycin, clarithromycin, and grapefruit juice. Adverse opioid-drug interactions from enzyme induction mostly involve CYP3A4 and, to a lesser extent, CYP2B6.

Morphine

Morphine is believed to possess a low potential for adverse drug interactions, because UGT inhibition produces few relevant pharmacokinetic changes in morphine or its metabolites [130].

Codeine

Analgesia requires the conversion of roughly 10% of codeine via CYP2D6 into morphine, which is then converted to M3G and M6G by glucuronidation. Codeine is also metabolized by CYP3A4 to the inactive metabolite norcodeine [103].

CYP3A4 inducers speed the conversion of codeine to the inactive norcodeine and decrease conversion to morphine. Although codeine undergoes phase II metabolism to codeine-6-glucuronide, UGT2B7 inhibition or induction does not result in codeine adverse drug interactions [130].

Oxycodone

Oxycodone undergoes a complex hepatic metabolic process. CYP2D6 catalyzes oxycodone to oxymorphone (10% of metabolites), and UGT2B7 rapidly inactivates oxymorphone by conversion to oxymorphone-6-glucuronide; the analgesic contribution of oxymorphone is minimal. CYP3A4 catalyzes oxycodone to noroxycodone, the primary (90%), but inactive, metabolite. In addition, CYP2D6 converts noroxycodone to noroxymorphone. These metabolites have varying mu receptor potencies and affinities [99; 176].

Many adverse drug interactions have been reported between oxycodone and other CYP3A4 substrates. CYP3A4 inhibitors can substantially increase oxycodone serum levels, reflected in the "black box warning" to not use oxycodone with CYP3A4 inhibitors due to the elevated risk of serious adverse effects, including potentially fatal respiratory depression. CYP3A4 inhibitors may elevate plasma oxymorphone to increase opioid effects, while CYP3A4 inducers may substantially decrease oxycodone (and potentially oxymorphone) serum levels, leading to analgesic failure. In general, concurrent use of oxycodone with CYP3A4 inhibitors or inducers is likely to result in adverse drug interactions.

The clinical effects of CYP2D6-mediated drug interactions with oxycodone are mixed, because overall analgesic contribution from the active metabolite oxymorphone is minimal [130].

Oxymorphone

Oxymorphone undergoes hepatic metabolism by phase II conjugation via glucuronide UGT2B7. The absence of CYP450 involvement minimizes adverse drug interactions with CYP substrates [115].

Hydrocodone

Limited clinical data have been published on drug interactions with hydrocodone metabolism. The overall evidence suggests concurrent use of CYP2D6 inhibitors diminish conversion of hydrocodone into the active metabolite hydromorphone [130].

Hydromorphone

The metabolites of hydromorphone are not thought to contribute to its pharmacologic activity. Minimal CYP450 involvement indicates a lack of adverse drug interactions impacting its pharmacokinetics [16; 115].

Fentanyl

Fentanyl is metabolized primarily via hepatic CYP3A4 and is a weak CYP3A4 inhibitor. As such, many CYP3A4 substrates can interact with fentanyl. Elevated plasma fentanyl and decreased fentanyl clearance can result from coingestion of CYP3A4 inhibitors. CYP3A4 inducers can diminish fentanyl serum levels and analgesia and increase clearance. The adverse interactions between fentanyl and CYP3A4 inhibitors are potentially very serious, and a "black box warning" on all fentanyl products cautions against concurrent use of fentanyl and all CYP3A4 inhibitors because of the heightened risk of adverse effects, including fatal respiratory depression. CYP3A4 inducers may nullify fentanyl analgesia, and patients receiving fentanyl should avoid all CYP3A4 substrates [130].

Methadone

Methadone is associated with numerous potentially serious adverse drug interactions. CYP3A4 inhibitors can delay methadone clearance and potentially lead to toxicity. Methadone has been linked to the development of the ventricular arrhythmia torsades de pointes; additional reports suggest an association between methadone-induced torsades de pointes and CYP3A4 inhibition [130; 177].

CYP3A4 inducers can reduce plasma methadone levels, leading to analgesic failure and opioid withdrawal. CYP2B6 inhibitors can decrease methadone metabolism to increase side effect risk, while CYP2B6 inducers delay metabolism to diminish its therapeutic effects [130; 177].

Many members of specific drug classes adversely interact with methadone, and clinicians should carefully evaluate the interaction potential of any CYP3A4 or CYP2D6 inhibitor used with methadone [130; 177].

The complex pharmacology of methadone makes the drug hazardous when prescribed without extensive knowledge and experience. With a half-life (15 to 60 or more hours) longer than analgesia (4 to 8 hours), risks of accumulation and fatal overdose are increased, as when analgesia wears off and pain returns followed by re-dosing. Other factors that contribute to the risk of toxicity include [49]:

- Metabolism by numerous CYP isoenzymes, which elevates the risks of drug-drug interactions, delayed clearance, and increased serum concentrations of methadone to fatal levels
- Prolongation of QTc interval, which may increase risk of life-threatening cardiac arrhythmias
- P-glycoprotein (P-gp) substrate, elevating risk of drug interactions that accelerate methadone blood-brain barrier penetration

Methadone requires metabolism by at least five fully active CYP450 isoenzymes for its efficient breakdown and elimination. This makes it the opioid with greatest susceptibility to adverse drug interaction. Concurrent use of common medications such as benzodiazepines, antihistamines, antidepressants, and antiviral agents may result in inhibition of CYP450-mediated breakdown and clearance of methadone, increased plasma levels, and serious risk of oversedation and suppression of CNS respiratory centers [175].

Toxicity risks of methadone can be mitigated with gradual titration and dose adjustment. Opioid-naïve patients should be started at a low dose, usually 2.5 mg every eight hours. The dose may be titrated by 10% to 20% increments, not less than three to four days apart except under inpatient or closely supervised settings. Once-daily methadone is ineffective for chronic pain; dosing at least every eight hours is required. When rotating patients from another opioid to methadone, it is important to consult the latest product information for dose equivalence and conversion; do not use published equianalgesic tables [103; 175].

The increasing use of methadone treatment for chronic pain has led to high rates of fatal toxicity and concerns over its safe and appropriate use as an analgesic. Clinical practice guidelines have been developed to promote safer methadone prescribing for chronic pain [178]. The first step is careful patient assessment. From a thorough history, medical records review, physical examination, and possibly electrocardiography, stratify patients on risk for substance abuse, adverse reactions with other prescribed medications, and arrhythmia. Alternative opioids should be used in patients at high risk of QTc interval prolongation. If methadone is used, a low starting dose and slow titration are necessary, as are diligent monitoring and patient follow-up. All patients should receive education on methadone safety.

Levorphanol

No adverse interactions with CYP450 substrates have been noted with levorphanol. Interactions at glucuronidation enzyme sites are theoretically possible, but none have been substantiated [16].

Tramadol

CYP2D6 and CYP3A4 account for more than 70% of tramadol metabolism. CYP2D6 inhibitors reduce tramadol analgesia and concurrent use should be avoided. CYP3A4 inhibitors may increase exposure to tramadol, and their use should be avoided. CYP3A4 inducers can reduce plasma tramadol, and patients requiring CYP3A4-inducing medications should be monitored for inadequate analgesia [130].

Tapentadol

Clinically relevant drug interactions are unlikely with tapentadol [179].

PHARMACODYNAMIC DRUG-DRUG INTERACTIONS

Pharmacodynamic drug-drug interactions are possible with all opioid analgesics. Drugs with hypoventilatory or CNS depressant properties, such as benzodiazepines, sedative-hypnotics, and antihistamines, can act synergistically with opioids to increase sedation and risk of potentially lethal respiratory depression [174].

Some pharmacodynamic adverse drug interactions with opioids can be clinically advantageous. For instance, ibuprofen co-administration with hydrocodone or oxycodone potentiates the analgesia of the opioids in laboratory-induced moderate-to-severe pain, producing a 2.5-fold and 4.6-fold shift in the effective dose, respectively. Aspirin and ketorolac have no effect on hydrocodone analgesia, and ibuprofen has no effect on fentanyl or morphine analgesia [180].

CDC GUIDELINES FOR OPIOID PRESCRIBING IN CHRONIC PAIN

In 2016, the CDC published opioid prescribing guidelines for chronic pain by primary care physicians, not applicable to active cancer treatment, palliative care, or end-of-life care [42]. The CDC guidelines are expected to have a significant effect on opioid prescribing. Release of the draft and final CDC guidelines provoked controversy and alarm from pain professionals and pain patient advocacy groups and serious concerns by the American Medical Association (AMA), the American Cancer Society (ACS), the American Academy of Pain Medicine (AAPM), and other prominent organizations [56; 57].

The public health issue of opioid analgesics is complex; the ideal is balancing opioid control and access. Overemphasis on access in the 1990s and early 2000s led to over-prescribing, increased addiction, and overdose; now, excessive control has the potential to lead to restricted access and undertreated and untreated chronic pain. The well-intentioned but narrow public health focus on curtailing opioid prescribing and patient access is consistent with the CDC's orientation and agenda, but it may not be the most helpful approach in patient care [5; 57].

In response to concerns raised and challenges encountered following implementation of the 2016 guidelines, in 2019 the CDC issued a clarification and cautioned against misapplication of the opioid prescribing guidelines in ways that could put patients at risk [25]. Specifically, the CDC advisory emphasized that the guidelines do not apply to patients under cancer treatment and those experiencing acute sickle cell crises, nor to patients with postsurgical pain; further, the dosage recommendation was not intended to impose hard limits or lead to "cutting off" of opioids or abrupt

tapering of opioids already prescribed at higher dosages. Finally, the guideline dosage recommendation should not be applied to patients receiving or starting medication-assisted treatment for opioid use disorder.

The CDC guidelines were based on a systematic review that rejected opioid studies greater than one year in duration without randomized controlled design. This made the pool of evaluable studies essentially unchanged from a 2009 systematic review of opioid analgesics, but conclusions of the 2009 review markedly differed from the 2016 review [5].

It is also important to note that the NPS, a comprehensive action plan to decrease the burden of undertreated pain, was also released in 2016. The NPS was developed in response to the 2011 IOM mandate for system-wide transformation of pain care but was largely overshadowed by the CDC guideline release [58].

The following recommendations are reprinted from the CDC guidelines and represent a simple approach to opioid prescribing for chronic pain. While this may be helpful for primary care providers, it does not take into account many of the nuances of opioid use for chronic pain, including patient-specific response, side effects, comorbidities, and pharmacokinetics and pharmacodynamics. These issues will be discussed in detail later in this course.

WHEN TO INITIATE OR CONTINUE OPIOIDS

Nonpharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain [42]. Clinicians should consider opioid therapy only if expected benefits for pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. Before starting opioid therapy for chronic pain, clinicians should, for all patients:

- Establish treatment goals for pain and function.
- Consider how therapy will be discontinued if benefits do not outweigh risks.
- Continue opioid therapy only if clinically meaningful improvement in pain and function outweighs safety risks.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians asserts that a robust agreement, which is followed by all parties, is essential prior to initiating and maintaining opioid therapy, as such agreements reduce overuse, misuse, abuse, and diversion.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed May 13, 2020.)

Level of Evidence: III (Evidence obtained from at least one relevant, high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies)

Before starting opioid therapy and periodically during the course of treatment, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

OPIOID SELECTION, DOSAGE, DURATION, FOLLOW-UP, AND DISCONTINUATION

When starting opioid therapy for chronic pain, clinicians should prescribe SA instead of ER or long-acting (LA) opioid formulations. When opioids are started, clinicians should prescribe the lowest effective dosage but use caution at any dosage. It is important to carefully reassess evidence of benefits and risks when increasing dosage to ≥50 mg MED/day. Prescribers should avoid or carefully justify increasing the dosage to ≥90 mg MED/day.

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids. It is important to prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

Clinicians should evaluate benefits and harms with patients within one to four weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should also evaluate benefits and harms of continued therapy with patients at least every three months. If benefits do not outweigh harms of continued opioid therapy, clinicians should taper and discontinue opioids or optimize other therapies and work with patients to taper opioids to lower dosages.

ASSESSING RISK AND ADDRESSING HARMS OF OPIOID USE

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms and incorporate into the management plan strategies to mitigate risk. Offering a naloxone kit should be considered when factors are present that increase opioid overdose risk, including:

- History of overdose or substance use disorder
- Higher opioid dosages (≥50 mg MED/day)
- Concurrent benzodiazepine use

Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. The patient's history of controlled substance prescriptions should be reviewed using state prescription drug monitoring program data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review prescription drug monitoring program data when starting opioid therapy for chronic pain, and periodically during opioid therapy for chronic pain, ranging from every prescription to every three months.

When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy, and consider urine drug testing at least annually to assess for prescribed medications, other controlled prescription drugs, and illicit drugs. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorders.

According to the American Society of Interventional Pain Physicians, presumptive urine drug testing should be implemented at initiation of opioid therapy, along with subsequent use as adherence monitoring, using in-office point-of-service testing, followed by confirmation with chromatography/mass spectrometry for accuracy in select cases, to identify patients who are noncompliant or abusing prescription drugs or illicit drugs. Urine drug testing may decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed May 13, 2020.)

Level of Evidence: III (Evidence obtained from at least one relevant, high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies)

CRITICAL RESPONSE TO CDC GUIDELINES

Experts have argued that the dose levels established in the CDC guideline are arbitrary. Millions of Americans currently receive 90 mg MED/day for needed pain control [56]. The true risk factors for toxicity and overdose include organ dysfunction, pain control, tolerance, drug interactions, psychiatric disorders, history of substance use disorder, genetic variation, and concurrent benzodiazepine/other CNS sedative use [6]. Critics have also asserted that the guideline neglects to mention the serious consequences from undertreated chronic pain [59].

In addition, the opioid dosing limits for acute pain were based on emergency department prescribing guidelines for non-traumatic, nonsurgical pain, to provide analgesia until the acute pain resolves or the patient sees his or her primary care provider [5]. As such, the recommendation is unlikely to be helpful in a chronic pain guideline.

GENERAL RECOMMENDATIONS FOR ANALGESIC PRESCRIBING

As discussed, the CDC's opioid prescribing guidelines are strictly focused on curtailment and, as such, are less useful for guiding analgesic selection or patient matching [5]. Instead, this information may be obtained from practice guidelines from the FDA, the Federation of State Medical Boards, and the AAPM. These organizations state that opioid analgesics are generally not used as first-line analgesic therapy; non-drug and non-opioid drug alternatives should be considered first. Opioids may be initiated when benefits are likely to outweigh risks, when other approaches to analgesia are ineffective or unlikely to be effective, and with a treatment plan reasonably designed to mitigate the risks of addiction, toxicity, and other adverse effects [20; 181; 182].

The American Society of Interventional Pain Physicians recommends screening for opioid abuse, as it will potentially identify opioid abusers and reduce opioid abuse.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed May 13, 2020.)

Level of Evidence: II (Evidence obtained from at least one relevant, high-quality randomized controlled trial or multiple relevant moderate- or low-quality randomized controlled trials)

Opioid therapy should be presented as a time-limited trial to evaluate pain, functioning and quality of life benefits, and adverse effects. Opioid-naïve patients should be started at the lowest dose, with titration to effect. In general, it is best to begin opioid therapy with an SA formulation and rotate to an ER/LA formulation, if indicated. Opioid therapy may be continued beyond the trial period after careful evaluation of benefits versus adverse effects and/or potential risks [20; 182].

Fear of inducing respiratory depression has constrained opioid prescribing for patients with chronic pain, but this risk can be minimized by exercising caution and providing patient education regarding the risks of any concomitant use of CNS depressants, especially benzodiazepines and alcohol [20]. Caution should also be used with dosing and titration in patients with sleep apnea or end-stage respiratory disease. Emerging data suggest an association of chronic opioid therapy with central sleep apnea, but the direction and details of this association are unclear. Patients on long-term opioid therapy are at risk for hypoxia if respiratory infections or acute asthmatic attacks supervene; patients should be advised that opioid dosage adjustments may be necessary in the event of any intercurrent illness that affects breathing.

Previous assumptions that patients on chronic opioid therapy will invariably develop analgesic tolerance (i.e., decreasing pain control with the same dosage over time) have also constrained effective opioid prescribing practices. Chronic pain unresponsive to opioid dose escalation may reflect tolerance, but it may also be the result of disease progression, non-opioid responsive pain syndromes, or opioid-induced hyperalgesia. Tolerance is not usually an impediment to long-term opioid therapy [20].

The most recent comprehensive guidelines for neuropathic pain were published by the Canadian Pain Society in 2014. Common causes of peripheral neuropathic pain include diabetic neuropathy; postherpetic neuralgia; post-thoracotomy, post-breast surgery, and post-back surgery pain; phantom limb pain; and complex regional pain syndrome [183]. ER opioid analgesics are recommended as second-line options for moderate-to-severe neuropathic pain.

Although there are few class-wide contraindications for the use of mu opioid agonist analgesics, contraindications to ER/LA opioid prescribing exist by formulation and specific opioid [181]. Contraindications to any use of opioid analgesics include [184]:

- Respiratory instability
- Acute psychiatric instability
- Uncontrolled suicide risk
- Active, untreated alcohol or substance use disorder
- True opioid allergy
- Current medication use with potential for dangerous drug interactions
- Active diversion
- Prolonged QTc (≥500 ms) (with methadone)
- Codeine (in pediatric patients)

Contraindications to long-term opioid analgesic therapy include [39; 185]:

- Primary headache
- Functional disorders
- Fibromyalgia syndrome (except tramadol)
- Chronic pain as prominent manifestation of a mental disorder (e.g., atypical depression, generalized anxiety disorder, post-traumatic stress disorder)
- Chronic pancreatitis, with the possible exception of brief (less than four weeks) treatment during an acute episode
- Chronic inflammatory bowel disease, with the possible exception of brief (less than four weeks) treatment during an acute episode
- Comorbid severe affective disorder and/or suicidality
- Current prescribed opioid abuse, diversion, and/or serious doubts over responsible use (e.g., unable to control opioid use, unwilling or unable to adhere to dosing schedule)
- Current or planned pregnancy

PATIENT FACTORS AND OPIOID ANALGESIC RESPONSE

Clinicians have long observed wide response variation in patients receiving opioids for pain. Patient factors, including age, medical comorbidity, and genetic differences, substantially contribute to this variation. Understanding how these factors influence opioid response can facilitate opioid selection and prescribing that mitigates side effects and toxicity while attaining adequate pain control.

AGE

By 2025, the number of adults 65 years of age and older in the United States is projected to increase 80% from 2010 estimates, comprising nearly 20% of the population. Understanding age-related physiologic changes and the complexity of pain management in elderly patients is essential for optimal efficacy, safety, and tolerability [49].

CLINICAL RELEVANCE OF AGE-RELATED PHYSIOLOGIC CHANGES	
Age-Related Change	**Clinical Relevance**
Pharmacokinetic Impact	
Reduced GI function and delayed absorption	Increased risk of opioid-related GI side effects Alteration of drug absorption (little clinical effect)
Altered distribution	Reduced distribution of water-soluble drugs Longer effective half-life of lipid-soluble drugs Increased potential for drug-drug interactions
Reduced hepatic metabolism	Reduced first-pass metabolism Oxidative reactions (phase I) may be reduced, prolonging half-life Conjugation (phase II metabolism) usually preserved Difficult to predict exact individual effects
Reduced renal excretion	Accumulation and prolonged effects of drugs and metabolites
Pharmacodynamic Impact	
Decreased receptor density, increased receptor affinity	Increased sensitivity to therapeutic and side effects
Source: [188]	*Table 3*

Independent of disease morbidity, aging elevates the risk of adverse events and associated opioid toxicity (***Table 3***). The elderly account for 49% of all hospitalizations due to medication adverse effects [186]. A variety of age-related physiologic changes account for this, including diminished gastric secretions and intestinal dysmotility; vitamin D deficiency, loss of appetite, and poor nutrition; and decreased bone density. Increased arterial thickening and rigidity elevate cardiac risk, while decreased lung elasticity may exacerbate respiratory disorders. Neurons become less stress-resilient. Reduced hepatic and renal blood flow diminish metabolism and filtration, increasing the risk for toxic substance accumulation [186]. Patients with dementia and/or cognitive deficits may have communication problems or confusion that render expression of pain severity, therapeutic response, and/or side effects difficult [187].

In older adults, heightened sensitivity to adverse effects results from physiologic changes, drug interactions, and drug-disease interactions [189]. Aging is associated with higher steady-state concentrations of water-soluble drugs and increased half-life of fat-soluble drugs. Consequently, opioid use in older adults may necessitate a lower than usual dose or longer dosage interval in order to maintain an appropriate balance between analgesia and side effect risk [190]. Other functional changes and comorbidities that impact opioid pharmacokinetics may also influence patient response and tolerability. Therefore, the selection and prescribed dosage of opioids in elderly patients must be considered carefully [187].

Older adults are also more likely to be prescribed multiple medications for a variety of chronic and acute conditions. In some cases of multimorbidity and chronic conditions (e.g., hypertension), the use of multiple medications may be unavoidable if one is to follow best practice clinical guidelines; this is referred to as "appropriate polypharmacy." However, even when the prescription of multiple medications is warranted, it raises the risks of drug-drug interactions, compliance issues, and adverse effects.

Elderly adults are more likely than younger adults to experience significant chronic pain because of the higher prevalence of rheumatic diseases, orthopedic conditions, and other debilitating illnesses. In many cases, opioid therapy with optimum patient-treatment matching is the safest analgesic option for elderly patients compared with oral NSAIDs, acetaminophen, antidepressants, or anticonvulsants [49].

MEDICAL COMORBIDITIES

Comorbid medical or neuropsychiatric conditions can affect opioid response or tolerability by interfering with opioid metabolism, elimination, efficacy, and adherence. Many patients require polypharmacy, especially the elderly and patients with psychiatric illness, cancer, cardiovascular disease, diabetes, and other chronic illnesses. As discussed, polypharmacy elevates risks of drug interactions that reduce efficacy or increase toxicity [191].

Cardiovascular, cerebrovascular, and respiratory disease all impact susceptibility to respiratory depression, bradycardia, or hypotension. Neurologic or neuropsychiatric conditions such as dementia, brain injury, or psychiatric illness may render the patient more susceptible to adverse CNS effects from opioids, such as cognitive impairment or sedation [191]. The presence of significant cognitive or intellectual disabilities can accompany sensory or communication disorders to interfere with verbal or nonverbal communication of pain to healthcare providers. In these patients, chronic pain can manifest in behavioral challenges or gradual declines in function. Appropriate treatment can greatly improve patient quality of life and caregiver stress [71].

Hepatic Dysfunction

Opioid biotransformation occurs in the liver, and any significant impairment in hepatic function will delay the metabolism and prolong the effect of opioids and their metabolites. Generally, CYP-mediated metabolism is affected more than glucuronidation, although opioids solely metabolized by glucuronidation also show altered pharmacokinetics. Morphine clearance is reduced ≥25%, and hydromorphone plasma concentrations are increased four-fold [191]. As such, it is important to avoid using oxymorphone and tapentadol and to use hydromorphone and oxycodone with great caution in these patients. Fentanyl is the first-choice opioid in patients with serious liver disease. Buprenorphine is safe in patients with mild-to-moderate liver disease, and methadone can also be used safely [103]. All opioids should be used with extreme caution with lowest-dose initiation [191].

Renal Dysfunction

Renal impairment can interfere with clearance of opioids and metabolites, which may lead to serum concentrations rising to dangerous levels. Delayed morphine elimination can lead to respiratory depression, excitotoxicity, and/or neurotoxicity. In these patients, morphine, hydromorphone, tramadol, tapentadol, and codeine should be avoided. Oxymorphone and oxycodone may be used with great caution. Fentanyl should be considered as the opioid of first choice for patients with renal impairment, followed by buprenorphine and methadone [103]. All opioids should be started at a low dose and slowly titrated [191].

Cardiovascular Disease

In patients with heart failure, special care should be taken with methadone. Some patients prescribed methadone for chronic pain may be at increased risk for developing prolonged QT interval or may already have a congenital QT prolongation.

Tramadol is recommended ahead of NSAIDs for patients with significant cardiovascular risk, and the same can be argued for tapentadol. Fentanyl, morphine, or oxycodone should be considered for these patients, as none are significantly associated with QT prolongation [190].

PRIMARY PHARMACOGENETIC INFLUENCES IN OPIOID ANALGESIC RESPONSE		
Site of Activity	**Genes of Interest**	**Function**
CYP450	*CYP2D6*	Involved in metabolism of several opioids analgesics, including: • Codeine to morphine • Oxycodone to oxymorphone • Tramadol to *O*-desmethyltramadol • Hydrocodone to hydromorphone
P-gp	*ABCB1/MDR1*	Decreased P-gp expression and activity can affect brain opioid levels and increase toxicity risk
COMT	*COMT Val158Met* variant	May increase dopaminergic stimulation due to dysfunctional COMT activity, which upregulates mu opioid receptor expression and increases morphine efficacy
Mu opioid receptor	*OPRM1*	Codes the expression of higher mu opioid receptor binding affinity of b-endorphin
Kappa opioid receptor	*MC1R*	Sex-specific increase in pain perception and analgesic response via the kappa opioid receptor
COMT = Catechol-*O*-methyltransferase, P-gp = P-glycoprotein.		
Source: [184; 192]		*Table 4*

GENETIC FACTORS

Morphine, oxycodone, hydromorphone, and fentanyl have comparable population level efficacy but widely variable analgesic efficacy and tolerability at the individual level; the same drug/dose may be toxic in some patients and have little or no effect in others. For example, up to 30% of patients with cancer-related pain show poor morphine response from inadequate analgesia or intolerability, but most achieve pain control with alternative opioids. Genetic factors account for at least 25% of this response variation to opioids [99; 192]. Genetic variations with greatest confirmation and relevance to opioid kinetics and dynamics include CYP450 enzymes, P-gp transporter ABCB1, catechol-*O*-methyltransferase (COMT) enzymes, and cytokine gene promoters (***Table 4***).

P-glycoprotein (P-gp) transporter ABCB1

The P-gp transporter ABCB1, encoded by the *ABCB1* gene, regulates the cerebrospinal fluid and serum levels of drugs passing the blood-brain barrier. *ABCB1* polymorphism alters P-gp transporter expression and activity at the blood-brain barrier to influence drug concentrations, CNS parent drug/metabolite ratios, and adverse effects. The impact of polymorphic *ABCB1* varies with the particular opioid in use. With morphine, it is associated with increased systemic and CNS exposure and accumulation; with fentanyl, increased respiratory depression; and with oxycodone, greater pain reduction and adverse effects due to higher plasma concentrations [193].

Cytochrome P450 Enzymes

As discussed, CYP enzymes influence the concentration of circulating opioids. Polymorphism of genes that encode CYP isoenzymes can affect opioid metabolism by determining isoenzyme activity level [194]. Polymorphic *CYP2D6* is the most important genetic determinant of opioid response [1].

Phenotypic variations due to *CYP2D6* polymorphism are classed into four functional groups: poor, intermediate, extensive, and ultra-rapid metabolizers [175]. In the general population, polymorphic *CYP2D6* results in ultra-rapid metabolism in 7%, poor metabolism in 10%, intermediate metabolism in 35%, and extensive metabolism in 48%.

ETHNIC/RACIAL DISTRIBUTION OF POLYMORPHIC *CYP2D6*			
Ethnicity/Race	**Poor Metabolism**	**Intermediate Metabolism**	**Ultra-Rapid Metabolism**
White	5% to 10%	2% to 11%	0.8% to 4.3%
Asian	1% to 2%	51%	0.9%
Black/African American	2% to 4%	30%	N/A
Hispanic	2.2% to 6.6%	N/A	1.7%
N/A = Not available.			
Source: [193; 194; 195]			*Table 5*

In white individuals, 77% to 92% are *CYP2D6* extensive metabolizers. However, racial differences are found in polymorphic *CYP2D6* distribution, with greater effects seen in certain groups (***Table 5***) [194].

Inactive/Absent Activity (Poor Metabolizers)

In patients with *CYP2D6* polymorphism resulting in poor metabolism, the opioid cannot undergo metabolism and is eliminated unchanged. Absence of metabolic activity delays clearance and elevates plasma opioid concentration. This phenotype is hazardous and especially dangerous in opioid-naïve patients. Another effect is analgesic failure with pro-drugs, from the inability to convert to the active metabolite [175; 196].

Underactive Activity

In intermediate metabolizers, the isoenzyme functions at reduced activity level and the opioid is metabolized at a slower rate, delaying plasma clearance, elevating serum concentration, and increasing toxicity potential. In some patients, isoenzyme function is activated with high serum opioid concentration, but these patients have greater overall risk of adverse effects and require lower opioid dosing [175; 194].

Full Activity

The greatest proportion of the population has extensive (full) opioid metabolism ability. With isoenzyme activity fully functional, patients show expected opioid dose response and the expected rate of opioid metabolism [194; 197].

Overactive Activity

In overactive (ultra-rapid) metabolizers, accelerated opioid metabolism and clearance results in analgesic failure from serum concentrations not reaching analgesic threshold, leading to ongoing pain and frequent dose escalation to attain analgesia. Another effect is greatly reduced analgesic duration, as when an ER opioid normally providing 12 hours of analgesia is effective for only 4 hours [175; 194].

Mu Opioid Receptor-1 (OPRM1)

The mu opioid receptor is the primary site of action for opioid analgesics, encoded by the mu opioid receptor-1 (*OPRM1*) gene. The *OPRM1* polymorphism most consistently associated with opioid response is A118G, which results in higher mu opioid receptor binding affinity of beta-endorphins. Studies show a pattern of less analgesia (i.e., higher dose requirements for morphine, tramadol, and fentanyl) and fewer CNS and GI side effects in patients with this polymorphism, reflecting reduced mu opioid receptor sensitivity and higher drug concentrations required to displace beta-endorphin from the mu opioid receptor [193]. A study of genetic influences on oxycodone response also found variations in mu and delta opioid receptor genes that may explain differences in patient responses [198].

Catechol-O-Methyltransferase (COMT)

The COMT enzyme is responsible for inactivating catecholamines. The most widely studied variant is a nucleotide substitution that changes the amino acid from valine to methionine at codon 158 (*Val158Met*). This alteration reduces the enzymatic activity of COMT, and low COMT activity is associated with increased mu opioid receptor system sensitivity to morphine [184; 192].

Cytokines

Cytokines are vital for coordination of immune and inflammatory response and are broadly classed as pro-inflammatory or anti-inflammatory mediators. Polymorphic cytokine gene promoters are associated with greater pain severity and greater morphine dose requirements [184; 192].

Clinical Relevance

As discussed, there is patient-to-patient variability in the rate at which opioids are metabolized based on genetic phenotype. Patients who are poor or intermediate metabolizers achieve a therapeutic effect at low doses and are at higher risk of toxicity at usual doses of opioid. Patients who are rapid metabolizers require higher and more frequent opioid dosing in order to achieve and maintain plasma concentrations in the therapeutic range. Importantly, with opioid pro-drugs like codeine and tramadol, phenotypic influence on the pharmacokinetics of the primary analgesic metabolite is reversed [197; 199].

Following poor metabolic response to an opioid pro-drug or ultra-rapid metabolic response to a conventional opioid, patients may insist on the need for higher doses due to analgesic failure [195]. Clinicians should avoid assumptions of addiction, abuse, or drug seeking until further investigation clarifies the underlying cause of analgesic failure. This patient behavior may reflect a polymorphic-mediated pseudoaddiction. In patients who rapidly metabolize opioids and who develop physiologic dependence with long-term use, forced or arbitrary opioid reduction can be hazardous—serum opioid concentrations may drop too rapidly to a low or zero level and produce severe opioid withdrawal, pain rebound, and cardiovascular hyperactivity that, in older patients, carries some risk for cardiac arrest or stroke [175].

Codeine

As an inactive pro-drug that requires metabolism by CYP2D6 into morphine for analgesia, poor and intermediate metabolizers gain little to no analgesia from codeine. In contrast, ultra-rapid metabolizers can have dangerously high serum morphine levels with standard-dose codeine, because the codeine-to-morphine conversion progresses more rapidly and a higher overall proportion of codeine is converted to morphine. This can result in severe or life-threatening side effects [197].

Tramadol

Tramadol is also a pro-drug, and clinical response is significantly lower in poor metabolizers, who require at least 30% greater tramadol dosing than patients with normal CYP2D6 activity [145]. Concurrent use of CYP2D6 inhibitors further contributes to metabolic interference. Poor metabolizers show poor pain control and a four-fold need for rescue medication with tramadol, while ultra-rapid metabolizers have shown intoxication, serious adverse effects requiring hospitalization, respiratory depression requiring naloxone, and near-fatal cardiotoxicity [196].

Oxycodone

The biotransformation of oxycodone involves CYP2D6 and CYP3A4; the two isoenzymes are prominently linked by activity and metabolic byproduct [176]. As such, polymorphic *CYP2D6* significantly impacts oxycodone analgesia and toxicity. Ultra-rapid metabolizers experience

significantly greater analgesic effect and toxicity, while poor metabolizers experience minimal therapeutic or side effects. Concurrent use of CYP3A4 inhibitors dramatically elevates analgesic efficacy and toxicity with oxycodone. This effect is further exaggerated in ultra-rapid metabolizers, who risk serious side effects and potentially fatal respiratory depression; an alternative analgesic should be considered in these patients [176].

Hydrocodone

Poor metabolizers with *CYP2D6* polymorphism have a 10- to 20-fold lower rate of hydrocodone clearance and reduced production of the active metabolite hydromorphone [115]. Evidence suggests that there is a heightened risk of side effects and toxicity if these patients concurrently ingest CYP3A4 inhibitors [196].

Methadone

The CYP3A4 and CYP2B6 isoenzymes primarily contribute to methadone metabolism. So, methadone should be used with caution in patients concurrently taking CYP3A4 or CYP2B6 inhibitors [196].

ANTICIPATING FACTORS THAT ALTER PATIENT RESPONSE TO OPIOIDS

Basic guidelines have been established to prevent opioid toxicity and overdose due to factors that alter opioid pharmacokinetics [175; 190; 199]. Genetic testing to identify polymorphisms relevant to opioid analgesics is not commercially available or affordable. Instead, providers should screen all patients for *CYP450* polymorphism before prescribing an opioid by taking a medication history with an emphasis on side effects, therapeutic failure, beneficial effects, drug sensitivity requiring a low dose, and insensitivity requiring a high dose. For example, a history of inadequate response or marked side effects to codeine suggests that selecting an opioid not metabolized by CYP2D6 (e.g., tapentadol, morphine, fentanyl, oxymorphone) is warranted.

With suspected *CYP450* polymorphism or in patients requiring several non-opioid medications that interact with CYP2D6, CYP3A4, CYP2C9, or CYP2C19 isoenzymes, prescribers should select an opioid with a metabolic pathway that mostly bypasses the CYP450 system. These include hydromorphone, oxymorphone, levorphanol, and tapentadol. Oxymorphone is perhaps the safest, as it lacks CYP450 metabolism and has no active or toxic metabolites.

All patients prescribed opioid analgesics should receive education on the dangers of co-ingesting benzodiazepines, antidepressants, and agents or drug classes that are known CYP450 enzyme inhibitors.

OPIOID SELECTION, INITIATION, AND MANAGEMENT

Analgesic response, safety, and tolerability are highly influenced by the complex interplay of opioid and patient factors. These factors should be considered before selecting an opioid agent and initiating treatment.

OPIOID RESPONSIVENESS

Opioid responsiveness is defined as the "degree of analgesia achieved as the opioid dose is titrated to an endpoint, defined either by intolerable side effects or the occurrence of acceptable analgesia" [200]. Poor pain response to opioids is the result of intolerable side effect(s), inadequate analgesia, or both, despite dose escalation. When poor analgesic response is identified, the clinician should consider using adjuvant analgesics, switching opioids, changing the route of administration, or using NMDA receptor antagonists [103].

ER/LA OPIOID ANALGESIC PRODUCTS AND DOSES RESTRICTED TO OPIOID-TOLERANT PATIENTS		
Brand Name	**Generic Name**	**Doses Restricted to Opioid-Tolerant Patients**
Avinza	Morphine capsules	90 mg, 120 mg
Belbuca	Buprenorphine buccal film	>75 mcg film/day
Butrans	Transdermal buprenorphine	7.5, 10, 15, and 20 mcg/hr
Dolophine, Methadose	Methadone tablets	Refer to full prescribing information
Duragesic	Fentanyl transdermal system	All doses
Embeda	Morphine/naltrexone capsules	100 mg/4 mg
Exalgo	Hydromorphone tablets	All doses
Hysingla ER	Hydrocodone bitartrate tablets	Single-dose ≥80 mg
Kadian	Morphine capsules	100, 130, 150, and 200 mg
MorphaBond	Morphine tablets	100 mg
MS Contin	Morphine tablets	100 mg, 200 mg
Nucynta ER	Tapentadol tablets	No product-specific concerns
OxyContin	Oxycodone tablets	Single-dose >40 mg, daily dose >80 mg
Targiniq ER	Oxycodone/naloxone tablets	Single-dose >40 mg/20 mg, daily dose >80 mg/40 mg
Xtampza ER	Oxycodone capsules	Single-dose >40 mg, daily dose >80 mg
Zohydro ER	Hydrocodone bitartrate capsules	Single-dose >36 mg, daily dose >72 mg
ER = extended-release.		
Source: [181; 203]		*Table 6*

RECENT OPIOID EXPOSURE

An essential safety factor in opioid selection is current opioid exposure. Many ER/LA opioid formulations and transmucosal immediate-release fentanyl are explicitly prohibited from use in opioid-naïve patients due to the high risk of severe, potentially fatal respiratory depression [201]. Patients should be identified as opioid-tolerant before considering the use of these particular formulations.

The term "opioid-tolerant" differs from "opioid tolerance." Opioid tolerance is the physiologic adaptation to opioid exposure over time that manifests in reduced drug effect [157; 202]. On the other hand, a patient is considered opioid-tolerant after continuous opioid use for at least one week of at least 60 mg/day oral morphine, 25 mcg/hour transdermal fentanyl, 30 mg/day oral oxycodone, 8 mg/day oral hydromorphone, 25 mg/day oral oxymorphone, or an equianalgesic dose of another opioid [181]. ER/LA opioid analgesic products and dose levels restricted to opioid-tolerant patients are shown in ***Table 6***.

ROUTES OF ADMINISTRATION AND FORMULATIONS

As discussed, opioids are available for many routes of administration, including oral, rectal, SC, IV, transdermal, transmucosal, and intraspinal. The oral route of administration is simple, cost-effective, and preferred, and SA and ER formulations are available for most oral opioids [103]. SA opioids are used to control pain until reaching a steady state.

SC, IV, rectal, transdermal, transmucosal, or intraspinal routes of administration are used when patients cannot take oral medications. IM administration is contraindicated, as it lacks any pharmacokinetic advantage and is painful. SC delivery is relatively easy, effective, and safe. IV is useful when pain is severe or pain levels have acutely increased. Transdermal fentanyl preparations are effective for patients unable to take oral medications who have stable pain control. Transmucosal fentanyl is similar to IV administration in its rapid onset and is used for acute breakthrough pain. The intraspinal route of administration is either epidural or intrathecal. This is the most invasive mode of opioid delivery and requires specialist involvement, but it confers advantages in patients with significant dose-limiting adverse effects, because systemic exposure is circumvented. Intraspinal delivery allows adjuvant medications to be directly administered to the spinal cord [103].

ER/LA Opioid Formulations

Although SA opioids are effective for pain control in many clinical contexts, they are characterized by pharmacokinetic shortcomings that may interfere with achieving sustained analgesia. ER formulations were developed to circumvent these pharmacokinetic shortcomings. Transdermal formulations of fentanyl and buprenorphine avoid the extensive first-pass metabolism that limits bioavailability with oral opioids [1]. ER formulations also lack the acetaminophen or ibuprofen found in many SA codeine, hydrocodone, and oxycodone formulations. These non-opioid analgesics impose a daily dose ceiling because of toxicity risks [137].

Several high-potency oral opioids have been used for decades to treat moderate-to-severe pain, including morphine, oxycodone, hydromorphone, levorphanol, methadone, and oxymorphone [16]. Methadone and levorphanol are inherently long acting, while morphine, oxycodone, hydromorphone, and oxymorphone possess a short analgesic duration and plasma half-life that requires frequent administration to establish and maintain a satisfactory analgesic effect. Before the 1990s, high-potency opioids were primarily used in surgery and inpatient settings, because they required IV or IM administration [154]. Oral ER formulations of these opioids were introduced to fulfill the unmet need of outpatients with chronic or disabling pain who required continuous analgesia not achievable with SA formulations [204; 205].

The terminology used to describe delayed-release opioids can be confusing. Opioids formulated with a release-delaying mechanism have been designated as ER, continuous or controlled release (CR), or sustained-release (SR), but these terms lack specific definition. Methadone and levorphanol are termed LA opioids to distinguish their inherently longer analgesic duration from opioids reformulated with an ER mechanism [206]. Likewise, the original strong opioids with relatively brief analgesic duration have been termed immediate-release or IR, but SA is a more accurate designation. IR is better reserved for truly rapid-onset opioids such as transmucosal immediate-release fentanyl.

Absorption, distribution, and metabolism influence the duration and stability of opioid analgesia and are difficult to manipulate with SA opioids. ER formulations modify the kinetic behavior of the opioid without changing the pharmacodynamic characteristics in order to improve analgesia through prolonged plasma concentration, lower maximum and higher minimum concentration, reduced fluctuation in plasma concentration, and delayed time in reaching maximum concentration [207; 208]. These ER opioid kinetics are thought to allow pre-emptive pain control instead of attempting to control pain after it becomes established (i.e., "chasing the pain"). This reduces or eliminates gaps in analgesia when plasma levels decline before the next scheduled dosing; decreases sleep interruption, side effects, and early opioid withdrawal symptoms by improving adherence and decreasing dose frequency; and reduces abuse potential by decreasing reward and reinforcement from slower onset of effects [72; 154; 209].

Fluctuating analgesia levels achieved with SA opioids can result in a need to take the medications more frequently (for comfort). This can cause conditioned passive pill-taking behavior, which can discourage the patient from taking an active role in pain self-care. The enhanced analgesic coverage and adherence with ER opioids may improve assessment of changes in the underlying pain condition or the chronic pain state by reducing the confounding factor of analgesic fluctuation [137].

The theoretical advantages of ER over SA formulations have been difficult to demonstrate in randomized controlled trials. However, there have been some comparison trials that may give some insight into the basis for ER formulations. In one study, a patient adherence advantage was found with ER formulations versus SA opioids, which may translate into improved pain relief [206]. In patients with moderate or greater chronic pain, CR tramadol showed lower pain scores and higher patient and investigator efficacy ratings than SA tramadol [210]. In addition, the daily variations in pain control experienced with twice-daily morphine were not reported with once-daily dosing, and this correlated with stability in serum morphine concentrations [211].

Compared with three-times daily morphine, twice-daily morphine is superior in pain control, sleep quality, and physical and mental impairment. In one study, almost twice as many patients dropped out with three-times daily versus twice-daily morphine, with inadequate pain relief the primary reason [212]. Patients with moderate-to-severe cancer-related pain show significantly greater dropout rates with four-times daily oxycodone than with twice-daily oxycodone due to inadequate pain control and side effects [213]. Another study of patients with cancer pain reported significantly greater tiredness during initial titration with six-times daily morphine versus once-daily morphine [214].

A literature review found that ER formulations of morphine, oxymorphone, oxycodone, and tramadol promoted improvements in ability to fall asleep, sleep quality, sleep duration, and pain-related sleep disturbance compared with SA formulations [206]. Patients with osteoarthritis have shown significantly improved sleep quality scores with ER versus SA oxycodone and with once-daily compared with twice-daily morphine [215; 216].

The CDC recommends initiation of opioid therapy with an SA formulation, but no further discussion or guidance is given [28]. The FDA states that the use of ER/LA opioids is indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate [181]. To ensure that benefits outweigh risks and to reduce risks while preserving access to opioid analgesics, the FDA has implemented risk evaluation and mitigation strategies (REMS) for ER/LA opioid analgesics. The ER/LA REMS program consists of a core prescriber education component that stresses safe product use, patient safety information, and guidance on patient counseling. This REMS-compliant education is strongly encouraged but not mandatory [181].

Contraindications to ER/LA Opioid Formulations

Class-wide contraindications to ER/LA opioids include [181]:

- Concurrent alcohol use (can cause rapid opioid release and potentially fatal respiratory depression)
- Mild pain, short-term, or acute pain
- Use as pre-emptive analgesia
- Postsurgical pain
- As-needed use for intermittent pain
- Paralytic ileus
- Acute or severe bronchial asthma or hypercapnia
- Significant respiratory depression, unless resuscitative equipment and respiration monitors are available

In addition to contraindications for all ER/LA opioids, there are some agent-specific contraindications. For example, dosages greater than 1,600 mg/day of morphine ER (Avinza) should be avoided due to the risk of severe liver toxicity from the fumaric acid excipient. Oxycodone/naloxone ER (Targiniq) should not be used in patients with moderate or severe hepatic impairment. Tapentadol ER (Nucynta) is contraindicated in the presence of current or past 14-day MAOI use.

With postoperative, acute, or chronic intermittent pain, analgesia often requires frequent titration, and the two- to four-hour analgesic duration with SA hydrocodone, morphine, or oxycodone is more effective than ER formulations. SA opioids are also recommended in patients who are medically unstable or with highly variable pain intensity [15; 207; 209].

Treatment of moderate-to-severe persistent pain in opioid-naïve patients should be initiated with an SA opioid, with subsequent upward or downward dose adjustment until reaching adequate and tolerable analgesia [28]. When satisfactory analgesia and dose stability are achieved, the patient should be switched to an ER formulation of the initial opioid (assuming patient tolerability) [15; 177].

When switching from SA to ER formulations, patients should be advised not to expect the relatively rapid onset of relief they may be used to with the SA opioid. Analgesic benefit will become evident over time, and taking a second tablet to speed the onset of pain relief may lead to delayed toxicity or overdose. These medications should be stored securely, never shared, never chewed or crushed, and properly disposed of when no longer needed, as they contain large amounts of opioid and are potentially lethal if ingested by someone without tolerance or tampered with to cause rapid release of the contents [137].

DOSING

In clinical practice, patients may require more frequent dosing intervals with LA/ER opioids than recommended in product labeling by the manufacturer. For example, the labeling for CR oxycodone recommends every-12-hour dosing, but some studies have found that patients need a dose interval of 7 to 8 hours and that the majority of such patients are prescribed CR oxycodone three to four times daily [218; 219]. Other studies of patients with moderate-to-severe pain found the majority used CR morphine three to four times daily [220]. Transdermal fentanyl patch labeling recommends patch replacement every 72 hours, but in one study, close to 50% of patients required patch replacement every 24 or 48 hours [218; 220].

This disparity can be explained by how premarket drug evaluation studies obtain pharmacokinetic data used in postmarket product labeling. These data are usually obtained from phase I studies that evaluate kinetic behavior of the drug in younger, healthy volunteers free of medical and psychiatric comorbidity and other medication use. This eliminates most patient factors that alter the pharmacokinetics of the drug. Less often, analgesic pharmacokinetic data are obtained from clinical samples involving subjects with a given pain condition, free of other medical and psychiatric comorbidities and concurrent medication use. These tightly controlled conditions eliminate factors that could later confound postmarking clinical data, but this limits applicability of the results to typical patients in real-world settings. No single opioid dosing protocol can fit the characteristics of all patients to determine analgesic response, tolerability, and required dose frequency [221].

The FDA permits marketing of generic drugs when bioequivalence is shown. This parameter is met when serum levels of the active constituent fall within 80% to 125% of the original branded drug. The allowable variation in serum levels can be problematic in agents with a narrow therapeutic index. An added complexity is that FDA mainly relies on self-reported bioequivalence evaluation by the generic drug makers [221; 222].

DOSE TITRATION

Titration is the process of incremental dose change based on individual patient needs and responses. The dose is increased (escalated) or decreased (tapered) until a reasonable balance is reached between analgesia and tolerability. Gradual titration allows sufficient time to ensure that the patient obtains the fullest degree of analgesia possible at the current dosage before further escalation is considered [223]. Regardless of opioid or dose, titration should be individualized based on health and pain status, treatment goals, and previous opioid response. Side effects such as sedation or nausea can interfere with upward titration.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends advising patients undergoing dosage titration in a trial of opioid therapy to avoid engaging in dangerous activities, such as driving a motor vehicle or the use of heavy machinery, until a stable dosage is established and it is certain that the opioid dose does not cause sedation, as well as when taking opioids with alcohol, benzodiazepines, or other sedating drugs.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed May 13, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

Opioid titration is slower with ER than SA formulations. When transitioning from SA to ER formulations of the same opioid, the dose is based on the equivalent total daily dose [157].

OPIOID ROTATION OR SWITCHING

Pharmacologists formerly considered opioid analgesics interchangeable, on the basis of shared mu opioid receptor agonism, differing mainly by potency. In contrast, clinicians have long observed subtle but important pharmacologic differences in potency, efficacy, and tolerability [224]. It is now known that individual differences in mu opioid receptor expression and density contribute to this variation.

Opioid rotation exploits these pharmacologic differences and incomplete cross-tolerance among opioids and involves switching the current opioid or route of administration to improve efficiency and safety [173; 223]. Opioid rotation can be an effective strategy for overcoming analgesic failure, side effect intolerance, problematic drug interactions, opioid-induced hyperalgesia, change in clinical status, problems related to medication cost and/or availability, need for a different route of administration, and patient preference [173; 223; 225].

Equianalgesic-Dose Tables

Verbatim use of equianalgesic-dose tables for opioid rotation contributed to opioid analgesic deaths in the 2000s and prompted changes in opioid conversion methods to mitigate risk and improve safety [12]. These tables include calculations derived from single dosing in opioid-naïve patients and permit broad guidance only. To ensure safety, a new opioid should start 50% below the calculated comparable dose to compensate for variable opioid response and incomplete cross-tolerance. The new opioid is titrated using product-specific instructions, with SA opioids used for analgesic rescue in breakthrough pain until reaching up-titration [12; 20; 226].

Morphine is the reference against which other opioids are compared, and analgesic potency is calculated as dose equivalence to morphine (i.e., MED). ***Table 7*** shows a typical equianalgesic-dose table with figures validated for acute pain in opioid-naïve patients and conversions for opioid-tolerant patients [181].

OPIOID ANALGESIC APPROXIMATE DOSE EQUIVALENTS			
Opioid Analgesic	**Oral Dose**	**Parenteral Dose**	**Morphine Equipotency Ratio, Oral**
Morphine	30 mg	10 mg	Reference opioid
Codeine	200 mg	100 mg	Not established
Fentanyl (transdermal)	Not applicable	100 mcg	Not applicable
Hydrocodone (Zohydro ER)	30–45 mg	Not applicable	1.5:1
Hydromorphone (Exalgo ER)	8 mg	2 mg	5:1
Levorphanol	4 mg	2 mg	Not established
Oxycodone (OxyContin ER)	20–30 mg	10–15 mg	2:1
Source: [123; 181]			*Table 7*

Breakthrough Pain Management

Breakthrough pain has been defined as a sharply increased pain episode with otherwise stable, well-controlled pain. The incidence of breakthrough pain in patients with chronic cancer and noncancer pain is 50% to 90%, even with pain appropriately managed with around-the-clock opioid analgesic coverage [228; 229; 230]. Breakthrough pain types include spontaneous, incidental, and end-of-dose failure. It is important to minimize the use of medications to address breakthrough pain in patients with chronic pain by titrating the baseline opioid dose or using adjunctive agents. If necessary, a reasonable dose for breakthrough pain is 10% to 15% of the total daily opioid dose [184]. Transmucosal immediate-release fentanyl products may be considered if prevention and control of breakthrough pain is not achieved.

Pharmacokinetic factors determine the options for breakthrough pain treatment. Analgesics for breakthrough pain are ideally selected according to the time it takes to reach maximum serum concentration. This period depends on the route of administration, usually attained by 1 hour with oral, 30 minutes with SC, and 6 minutes with IV routes [103].

Despite the self-limited duration (mean: 30 to 60 minutes), breakthrough pain is highly distressing to the patient and burdensome to families, caregivers, and healthcare systems. It is linked to decreased functional status, treatment dissatisfaction, and worse medical outcomes. Breakthrough pain may go unrecognized and is often undertreated due to lack of knowledge and undue concern regarding overmedicating [231]. Of patients with breakthrough pain, 60% describe pain intensity as severe but only half take medication to address it [117]. Breakthrough pain has an unpredictable onset and reaches peak pain intensity in 5 to 15 minutes, making SA morphine, hydromorphone, and oxycodone—with onsets of action 30 minutes after oral ingestion—ineffective [143].

IV fentanyl analgesia, with onset of action in 5 to 8 minutes and duration of 30 to 60 minutes, is ideal but not feasible for outpatient breakthrough pain management. Instead, transmucosal immediate-release fentanyl products overcome the limitations of SA opioids to deliver analgesia approaching the rapid onset of IV fentanyl [231]. Available products include [201]:

- Sublingual tablet (Abstral)
- Citrate oral transmucosal lozenge (Actiq)
- Buccal tablet (Fentora)
- Nasal spray (Lazanda)
- Buccal soluble film (Onsolis)
- Sublingual spray (Subsys)

Transmucosal immediate-release fentanyl products have been shown superior in pain reduction to placebo at all time points from 15 to 60 minutes and to SA oral morphine in the initial 45 minutes. Among these products, intranasal fentanyl spray is possibly superior to the buccal tablet and oral transmucosal lozenge in the first 30 minutes of dosing [143].

Transmucosal immediate-release fentanyl products are highly potent, rapid-acting opioids, and their use by opioid-naïve persons can be fatal at any dose. To ensure that benefits outweigh risks, the FDA enacted a class-wide REMS that emphasizes appropriate product prescribing and dispensing to opioid-tolerant patients only. It is also important to avoid the inappropriate conversion between one transmucosal immediate-release fentanyl product and another and to safeguard against accidental exposure to children and others. The FDA recommends prescribers, pharmacists, and patients be educated on the safe use and risks of misuse, abuse, addiction, and fatal overdose associated with these products. The diverse routes of administration of transmucosal immediate-release fentanyl products allow greater matching of product with patient preference, often determined by disease and breakthrough pain characteristics [201].

Although often used off-label, transmucosal immediate-release fentanyl medications are only approved for breakthrough pain in adults (18 years of age or older) with cancer who are already receiving, and are tolerant to, regular opioid therapy for underlying persistent cancer pain [143; 231]. The exception is Actiq and generic equivalents, which are approved starting at 16 years of age. Even highly opioid-tolerant patients should start at the lowest available dose. Patients may need to switch between formulations to find the best match, but prescribers should never attempt this without guidance from specific product prescribing information, available on the FDA website at https://www.TIRFREMSaccess.com. This website should be consulted for all information regarding transmucosal immediate-release fentanyl products, including new and updated information [201].

Analgesic Failure

Pain control and tolerability in long-term opioid therapy may be hindered by the development of analgesic tolerance, opioid-induced hyperalgesia, oral opioid malabsorption, or HPA-axis dysfunction. One way to gauge the adequacy of pain control is to consider whether the use of added opioids has resulted in improvements in functioning, physical capacity, psychologic well-being, family/social interactions, and healthcare resource use, which are weighed against unwanted effects, such as daytime sedation, mental confusion, constipation, and other side effects.

Tolerance

Opioid tolerance and opioid-induced hyperalgesia are both characterized by diminishing pain control. However, tolerance may reflect decreased opioid sensitivity, while opioid-induced hyperalgesia represents increased pain sensitivity [232]. Etiologically, opioid tolerance reflects an adaptation to drug exposure over time that diminishes drug effect, though pain can generally be controlled with dose escalation. Opioid-induced hyperalgesia reflects a paradoxical increase in pain that may worsen with opioid up-titration [233; 234].

Tolerance to opioids may develop in several ways. Short-term use inhibits the production and release of endogenous opioids (e.g., beta-endorphins), while long-term use may also inhibit mu-opioid receptor expression. Studies of long-term morphine use have found down-regulation in *POMC* gene expression and subsequent decrease in endorphin production; decreased mu opioid receptor density on beta-endorphin containing neurons in the hypothalamus; and mu opioid receptor uncoupling from ligand-gated voltage channels with decreased

ion channel potency and efficacy [111]. Morphine analgesic tolerance may also result from increased production of the anti-opioid peptides that bind mu receptors to decrease opioid binding and activation of mu opioid receptors. These processes develop over time and correspond with patient requirements for increasing opioid dose to maintain analgesia [111].

Other mechanisms may contribute to the loss of opioid analgesia. Pharmacokinetic changes can accelerate opioid metabolism and elimination from up-regulation of enzymatic activity in the metabolic pathway for the opioid. With enzyme induction, plasma opioid concentration diminishes over time while dosing remains constant [233]. The addition of other medications can induce metabolizing enzymes, with accelerated breakdown and excretion of the opioid leading to loss of analgesia and the need for dose escalation to regain analgesia [235]. Pharmacodynamic processes that include activation of the NMDA receptor/nitric oxide cascade can also result in opioid hypoanalgesia. NMDA receptor or nitric oxide synthase blockade can prevent or reverse opioid tolerance [236; 237; 238].

Progression of the underlying pain condition can also increase pain intensity and require dose escalation to control the pain. This may be mistaken for pharmacologic tolerance [233]. In general, tolerance can be managed by opioid rotation, dose escalation, or adding a non-opioid analgesic [175].

Opioid-Induced Hyperalgesia

As noted, opioid-induced hyperalgesia is characterized by paradoxical pain amplification. Pain sensitivity is heightened in the absence of a new or exacerbated injury. Opioid-induced hyperalgesia should be suspected in the patient who reports an unusual or unexplained change in pain profile, a diffuse allodynia (i.e., pain from normally non-painful stimuli) not related to the original pain condition, or worsening pain in response to dose escalation [234; 239].

Opioid-induced hyperalgesia involves CNS and PNS sensitization that develops through multiple mechanisms, including NMDA receptor activation; increased spinal cord dynorphin levels that activate excitatory pro-nociceptive neuropeptides; and CNS glial cell activation [232; 233; 234; 240]. CNS pain facilitatory mechanisms contribute to hyperesthesia (i.e., exaggerated pain sensitivity) and allodynia. Pain abnormalities with opioid-induced hyperalgesia often reflect exacerbated pre-existing painful conditions, with pain intensity worse than before opioid therapy [232; 241]. However, patients often describe the pain as more diffuse, less defined in quality, and typically extending beyond the original painful areas. Many features of pain associated with opioid-induced hyperalgesia resemble the pain experienced during opioid withdrawal, and both share a common neurobiology [232].

The diagnosis of opioid-induced hyperalgesia is often made in association with an increase in the opioid dose. Pain reduction indicates opioid tolerance, while worsening pain indicates opioid-induced hyperalgesia. Conversely, reducing the opioid may alleviate opioid-induced hyperalgesia symptoms, although care should be taken to avoid inducing withdrawal symptoms, which can increase pain and cloud the clinical picture [232].

Opioid-induced hyperalgesia is managed by addressing the underlying mechanisms. Morphine has the highest risk of opioid-induced hyperalgesia and should be replaced, if appropriate, in these patients. Switching to an NMDA antagonist opioid (e.g., methadone, levorphanol) is one approach. Spinal dynorphin is a kappa opioid receptor agonist, and kappa receptor antagonism may reverse opioid-induced hyperalgesia. As such, the kappa receptor antagonist buprenorphine is uniquely helpful as an alternative opioid for opioid-induced hyperalgesia [232]. If neuropathic pain is the original condition, it will often preferentially respond to non-opioid analgesics such as amitriptyline or pregabalin, which can enhance analgesia and decrease opioid dosing [234].

The NMDA antagonist ketamine has been used successfully in outpatients with opioid-induced hyperalgesia and is perhaps the most effective agent [239]. There is also evidence that concurrent use of the opioid antagonists naltrexone or naloxone at ultra-low doses can prevent opioid-induced hyperalgesia and enhance analgesia [242].

Oral Opioids and GI Malabsorption

Malabsorption may also contribute to analgesic failure. Possible causes of oral opioid failure were studied in 95 patients with intractable pain [19]. Patients were initially screened to assess pain and functional improvement with oral opioids; 21.1% had three or more failed oral opioid trials. Malabsorption symptoms of nausea and steatorrhea were identified in 100%, and undigested medication in the stool detected in 70%. Pain relief from IV hydromorphone was experienced by 75%. The researchers concluded that patients with intractable pain and oral opioid failure may have a GI condition that interferes with absorption. These patients require non-oral routes until the GI dysfunction is resolved [19].

Endocrinopathy

Some patients with severe chronic pain lack analgesic response from lower-dose opioids; their complaints of analgesic failure may be dismissed despite severe impairment and debilitation. It is crucial to consider an underlying endocrinopathy as a possible cause. In one study of 61 patients with refractory chronic pain, 80.3% showed at least one hormone abnormality and 11.5% showed severe pituitary-adrenal-gonadal deficiency [243].

Pain that is uncontrolled, intractable, or severe impacts the endocrine system. Pain is a potent stressor that initially elevates serum pituitary, adrenal, and gonadal hormones. Severe uncontrolled pain depletes serum hormone levels; this serves as a biomarker for endocrinopathies and indicates that enhanced analgesia and hormone replacement may be necessary. Adequate physiologic levels of specific hormones may be required for optimal analgesia, neuroprotection, and neurogenesis. Hormone replacement is not a substitute for opioids but can minimize dose requirements [243].

Patient Nonadherence

Many patients with chronic pain do not take their medication as prescribed or stop altogether. A review of 11 trials involving 2,473 patients found an overall discontinuation rate of 22.9%, including 11.4% with weak opioids and 34.1% with strong opioids [244]. Community-based studies have found that 21% to 38% of patients adhere to their prescribed opioid regimens [245; 246].

Treatment adherence is essential for optimal pain control, for quality of life improvement, and to reduce healthcare utilization and associated costs. Inconsistent adherence to strong opioid prescriptions is the most important risk factor for hospitalization in these patients [247]. Poor adherence is also linked to problematic side effects, depression, higher dosing frequency, and negative attitudes of relatives or partners toward the patient's need for opioids. Adherence may be improved by patient education regarding the pain condition, realistic treatment expectations, and perceived benefit from treatment. In addition, primary care providers can modify risk factors for poor adherence by decreasing the dose frequency and addressing treatment expectation and benefit, side effects, depression, and attitudes of relatives and partners [248]. A tailored approach to opioid selection and titration optimizes the balance between pain control and side effects, which often enhances therapy adherence [1].

OPIOID ANALGESIC SIDE EFFECTS AND MANAGEMENT

All opioid analgesics have the potential for serious adverse effects when prescribed without careful consideration of patient factors. Even when prescribed with due diligence, patients may experience side effects that, if not anticipated or managed properly, can promote treatment discontinuation or analgesic failure from intolerance of therapeutic dosages. Side effects are generally adverse (with the possible exception of sleep-promoting sedation) and result from specific opioid pharmacology, patient age, comorbidities, genetic polymorphisms, and impaired hepatic or renal function [103].

Upon treatment with opioids, most patients report their pain is less intense, less distressing, or gone entirely, while other sensory perceptions are unchanged. A minority of patients experience euphoria, but it is more common for pain-free volunteers without a history of substance use disorder to describe morphine as unpleasant. Except in cases of acute intoxication, opioids, even highly potent mu agonists, seldom induce the loss of motor coordination or slurred speech characteristic of calming or sedating drugs [104; 249].

Clinicians should anticipate and monitor common opioid side effects and discuss these effects with patients before opioids are initiated. Many side effects are time-limited and lessen or resolve following stable dosing. Tolerance to opioid effects tends to develop at different rates, ranked below in descending order [175]:

- Euphoria (most rapid)
- Sedation
- Nausea
- Analgesia
- Constipation (late, if ever)

SEDATION

Sedation is a dose-dependent and often time-limited side effect. Anticholinergic activity of some opioids may contribute to sedation and drowsiness, but alleviation of pain can itself promote relaxation and sleep. Excessive sedation can occur with higher-dose initiation or rapid dose escalation and may result in nonadherence or reduced quality of life [110].

Management approaches for opioid-induced sedation include reduction or elimination of nonessential sedating medication (e.g., benzodiazepines, antihistamines, some TCAs, muscle relaxants), opioid dose reduction, and/or opioid rotation [110].

PRURITUS

Opioid analgesics can cause pruritus, which may be severe and difficult to manage, highly distressing to the patient, and among the top reasons for discontinuation. Pruritus is often misdiagnosed as an opioid allergic reaction, but true allergic and anaphylactic reaction to opioids is rare (<1%) and results from activation of central mu opioid, dopamine, serotonin, prostaglandin, and histamine receptors. Reactions related to histamine activation have been reported, most often with morphine. These reactions include urticaria, bronchospasm, and hypotension. When pruritus does occur, it typically involves the face, nose, and torso, and intrathecal administration is most associated with intense itching. Histamine release is most common with morphine [104; 250].

The goal of treating opioid-associated pruritus is to ameliorate the symptom without reversing analgesia with opioid antagonists. Options include anti-histamines (e.g., diphenhydramine, hydroxyzine) or H2 blockers (e.g., ranitidine, cimetidine). Naloxone infusion may be considered if other treatments fail and itching is severe. Opioid rotation to a different synthesis class (natural, semisynthetic, or synthetic) may also be successful. Epidural kappa opioid receptor agonists nalbuphine or butorpha-

nol can reverse pruritus from mu agonists while maintaining analgesia [110; 250; 251]. If a true opioid allergy is identified, the offending opioid should be replaced by an opioid from a different chemical class to avoid antibody recognition [128].

OPIOID-INDUCED CONSTIPATION AND BOWEL DYSFUNCTION

GI symptoms are among the most common side effects reported with opioid use. Providers should be alert to the character and extent of patient distress resulting from these effects and the potential for non-adherence to therapy. Opioid-induced bowel dysfunction takes various forms, including dry mouth, nausea, vomiting, gastric stasis, bloating, abdominal pain, and opioid-induced constipation. Opioid activation of mu and kappa receptors in the neuronal plexus of the gut wall increases intestinal wall and sphincter resting tone and reduces biliary, pancreatic, and intestinal secretions. This results in dysrhythmic, non-propulsive contractions (bowel spasm), delayed passage and increased viscosity of intestinal contents, and the onset of constipation. Spasm and colic can also result from increased biliary tract tone [105; 107].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends monitoring for side effects (e.g., constipation) and managing them appropriately, including discontinuation of opioids when indicated.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed May 13, 2020.)

Level of Evidence: I (Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness)

Up to 91% of patients taking opioids experience constipation, the most common opioid-induced bowel dysfunction symptom. Opioid-induced constipation, often in combination with chronic nausea, can cause considerable distress, greatly diminished quality of life, and opioid discontinuation by as many as 33% of patients [252]. Most patients require constipation management for the duration of opioid therapy because complete tolerance rarely develops [123].

In order to prevent opioid-induced constipation, a laxative bowel regimen and bowel management education should be provided to all patients prescribed an opioid. In the event of laxative or stool softener nonresponse, patients may try [123; 171]:

- Mild osmotic agents (70% sorbitol solution, lactulose, milk of magnesia)
- Polyethylene glycol
- Bulk-forming laxatives (psyllium) with proper liquid intake
- Mild cathartic laxatives (senna, bisacodyl)

Saline or tap water enemas may be necessary to avoid fecal impaction.

Opioid switching from a hydrophilic agent (e.g., morphine, oxycodone, hydromorphone) to a lipophilic opioid (e.g., fentanyl, buprenorphine, methadone) may be helpful, as there is greater GI opioid receptor activity with hydrophilic opioids. Peripherally acting mu opioid receptor antagonists are indicated when other opioid-induced constipation treatments fail, including methylnaltrexone (50% to 60% efficacy in severe refractory opioid-induced constipation) or subcutaneous naloxegol injections [171].

NAUSEA AND VOMITING

Roughly 33% to 66% of patients receiving opioids experience nausea and vomiting, usually during initiation and titration. This often resolves by the first week of treatment, but can recur later with a significant dose increase. Nausea and vomiting results from reduced GI motility and constipation, delayed gastric emptying, and activation of opioid receptors, dopamine tracts, and other transmitters in the chemoreceptor trigger zone [123]. Some patients report a sharp exacerbation of nausea upon movement, suggesting a component of opioid-induced vestibular dysfunction [105].

Nausea and vomiting during opioid initiation should be controlled with antiemetics, and these agents should be available as needed after dosing is stabilized. Metoclopramide and domperidone are first-line options due to a mechanism that improves GI motility. Around-the-clock and/or transdermal prescribing may be considered, with extra doses for rescue. Extrapyramidal symptoms may occur, but are considered infrequent [123; 253].

Antihistamines block histamine receptors in the vomiting center and on vestibular afferents. They may be used when [123; 253]:

- Vestibular sensitivity mimics motion-induced nausea
- GI prokinetic agents are contraindicated due to bowel obstruction

Ondansetron and other serotonin receptor antagonists are also effective in treating nausea and vomiting. Chlorpromazine is likely to produce significant sedation; prochlorperazine has greater antiemetic potency. However, potential extrapyramidal symptoms and anticholinergic side effects limit the clinical use of these agents [123; 253].

RESPIRATORY DEPRESSION

Therapeutic doses of morphine depress all phases of respiratory activity, including the breathing rate, minute volume, and tidal exchange. Respiratory depression results from decreased brainstem sensitivity to carbon dioxide build-up and is the primary lethal side effect of opioids [120]. Patients are most vulnerable to respiratory depression in the first five days of opioid initiation, especially the first 24 hours. Risk factors include obesity, sleep apnea, and pre-existing respiratory disorders (e.g., acute asthma, respiratory infection). Respiratory depression is antagonized by pain, and patients with substantial pain relief following uncontrolled pain are also at risk. Coingestion of any CNS respiratory depressant, including benzodiazepines or alcohol, elevates the risk of pronounced respiratory depression and fatality [104; 254].

Opioid use at appropriate prescribed doses seldom results in significant respiratory depression, even in patients with end-stage chronic obstructive pulmonary disease or dyspnea from advanced-stage cancer [255]. Patients on stable-dose, long-term opioid therapy have low risk of respiratory depression, although concerns remain prevalent among clinicians and patients [123]. It is important to note that respiratory depression may occur with a change in opioid analgesic, rapid dose escalation, development of renal failure or a serious pulmonary condition, or a single, large, inappropriate dose [254].

Sedation always precedes respiratory depression. With fatal respiratory depression, the process begins with sedation followed by reduction and finally cessation of breathing over the course of 5 to 15 minutes. Respiratory depression is characterized by rising peripheral carbon dioxide pressure, falling peripheral oxygen, and decreasing respiratory rate [255]. While these laboratory markers directly measure ventilation and ventilatory drive, they are often only available in an inpatient setting. In the outpatient setting, breathing rate and/or oxygen saturation are surrogate measures of ventilatory drive. In these cases, severe respiratory depression is defined by a respiratory rate less than 8 to 10 breaths per minute and oxygen saturation of <85% for more than six minutes per hour [120].

Naloxone can reverse respiratory depression caused by most opioids (though it is ineffective with meperidine). The extent and duration of naloxone reversal is determined by the specific opioid and dose, route of administration, concurrent medication(s), underlying disease, pain and state of arousal, and genetic factors [120].

When indicated for reversal of opioid-induced respiratory depression, naloxone (1:10 dilution) titrated in small increments or given by infusion should be administered to improve respiratory function without reversing analgesia [255]. The patient should be monitored carefully until the respiratory depression episode resolves [123].

Naloxone should be administered cautiously by slow IV infusion in opioid-dependent patients because it can abruptly induce acute opioid withdrawal syndrome and precipitate severe uncontrollable pain. Given this potential for abrupt, overwhelming physiologic and emotional stress with naloxone intervention, its use in respiratory depression should be strictly limited to patients unresponsive to physical or verbal stimulation or patients with shallow respirations, respiratory rate less than seven breaths per minute, or pinpoint pupils [120]. The 30- to 81-minute duration of naloxone is less than most mu opioid agonists, and re-administration is usually required.

The unique properties of nalbuphine make it effective in reversing opioid-induced respiratory depression or pruritus while maintaining analgesia. Nalbuphine can be a good analgesic option for patients susceptible to severe respiratory depression, pruritus, or nausea and vomiting with standard opioids [110].

SEROTONIN SYNDROME

Serotonin syndrome results from overactivation of central and peripheral serotonin receptors, usually from concurrent use of multiple serotonergic agents. Serotonin syndrome can result from drugs that influence the reuptake, metabolism, synthesis, or release of serotonin; influence serotonin receptor activity; or interfere with CYP2D6 or CYP3A4 metabolism. The most commonly implicated agents are SSRIs, but other medications that may affect serotonin levels include serotonin-norepinephrine reuptake inhibitors, MAOIs, antipsychotics, analgesics, antiemetics, cough suppressants, and dietary supplements. In more severe cases, patients develop hyperthermia, autonomic instability, delirium, and muscle rigidity, with complications including seizure, rhabdomyolysis, arrhythmias, and respiratory arrest. Suspicion of serotonin syndrome requires urgent emergency management [256; 257].

Tramadol is the only opioid analgesic associated with serotonin syndrome. SSRIs inhibit CYP2D6, which decreases tramadol analgesic efficacy. Concurrent use of tramadol and paroxetine or venlafaxine has been reported to cause serotonin syndrome [256; 257]. Genetic susceptibility to serotonin syndrome has been identified and is influenced by a patient's ability to produce different ratios of positive and negative tramadol enantiomers [257].

NEONATAL ABSTINENCE SYNDROME

Teratogenic effects from opioid exposure during pregnancy have not been identified. However, chronic opioid use during pregnancy can result in physical dependence in utero and potentially life-threatening opioid withdrawal in the neonate at birth and for up to 12 days after [104].

If signs of neonatal abstinence syndrome are present, the neonate should be taken to intensive care for observation and further assessment. Opioid replacement may be necessary to stabilize the patient, reverse the syndrome, and reduce complications of withdrawal. Additional medications may be necessary to control seizures and other symptoms.

MORPHINE AND CARDIAC RISK

Morphine is commonly used for chest pain in patients with a suspected acute coronary syndrome, but data suggest morphine use in patients with unstable angina and non-ST segment elevation myocardial infarction may increase mortality. It should be used with great caution or avoided entirely in this patient group [258].

NEUROPSYCHIATRIC EFFECTS

Hallucinations are more strongly associated with mixed agonist/antagonist opioids and rarely occur with mu opioid agonists, with few exceptions. In fact, a review concluded that mu receptor agonist opioids were not only free of psychoses risk, but probably possesses antipsychotic activity yet to be characterized [259].

Other adverse CNS effects, including cognitive impairment, delirium, and generalized myoclonus, are associated with meperidine, morphine, or hydromorphone use in patients with renal impairment. In these patients, opioid metabolites accumulate to neurotoxic levels. The metabolites have anticholinergic activity, which can result in cognitive changes and delirium [123].

There is little research that sufficiently addresses brain response to chronic opioid therapy. Positron emission tomography and magnetic resonance imaging studies show changes in brain response to long-term opioid therapy in patients with chronic pain. However, it is unclear whether these neuroimaging findings are the result of the chronic pain or the opioid medication use [260].

Differential diagnosis is necessary in patients with suspected opioid-induced delirium to rule out dehydration, other CNS medications, sepsis, and hypercalcemia. Tactile hallucinations and myoclonus suggest opioid toxicity. Immediate delirium management consists of neuroleptics to control agitation and perceptual or delusional disturbances. Haloperidol is the first-line option; methotrimeprazine and chlorpromazine are alternative options, especially when sedation is beneficial. For resistant delirium, midazolam is preferred; lorazepam is used for comorbid anxiety. In cases of cognitive impairment in the absence of delirium, methylphenidate or modafinil may be used. These agents are not recommended with evidence of perceptual or delusional disturbances [123].

Opioid toxicity from accumulating neurotoxic metabolites may present with generalized myoclonus, sedation, confusion, or chronic nausea. This is generally resolved by opioid switching [123].

IMMUNOLOGIC CHANGES

The traditional view of opioids as immunosuppressive has been challenged by evidence showing a more complex role of opioid receptors in immune function. Different opioids or routes of administration act through different mechanisms to produce immunosuppressive, immunostimulatory, or dual immune effects. The impact of specific opioids on immune function probably result from a combination of direct effects on immunocytes and indirect effects on centrally mediated mechanisms, systemic production, and release of immunomodulatory mediators [261].

The interaction between opioids and the immune system is complex. Trauma and severe pain alone are immunosuppressive, which is reversible by sufficient pain control [262]. Exogenous opioid drugs can induce immunosuppression, while endogenous opioids appear to promote immunoactivation.

Opioid therapy has been shown to inhibit humoral and cellular immune responses, including antibody production, lymphocyte activity, cytokine expression, and phagocytic activity. Potential underlying mechanisms include HPA modulation, sympathetic nervous system stimulation, and activation of mu opioid receptor on immune cells [263; 264]. Opioids vary by immune system interaction. Compared with morphine, tramadol produces greater enhancement in natural killer cell activity, lymphocyte proliferation, and interleukin-2 release, while buprenorphine produces a negligible effect on immune response [249].

ENDOCRINE EFFECTS

Opioid therapy can result in HPA suppression and hypopituitarism, clinically expressed as hypogonadism, impotence, infertility, and/or osteoporosis [265]. Opioid-induced hormone dysfunction has been observed in men and women with oral, transdermal, IV, and intrathecal administration [249].

Opioids appear to differ in degree of adverse effect on hormonal function. In one study, men receiving buprenorphine maintenance therapy for opioid addiction showed significantly higher plasma testosterone levels and less sexual dysfunction than those receiving methadone [266]. Although long-term opioid therapy produces a dose-dependent decrease in total and free testosterone level, serum hormone levels return to normal in both sexes shortly after opioid cessation. Not all men experience androgenic suppression with long-term opioid therapy; body mass index and smoking status are thought to increase the risk of opioid-induced hormonal dysfunction [249].

If a patient on opioid therapy complains of changes in libido or sexual dysfunction, treatment is empirical, with knowledge that multiple factors may be involved in the pathogenesis of sexual dysfunction. In these cases, non-opioid analgesics should be added to reduce or, if possible, discontinue the opioid. In men, testosterone replacement is indicated if serum testosterone is low and not contraindicated. Sildenafil or another phosphodiesterase type 5 inhibitor may be used for men experiencing sexual side effects [121; 123].

For women taking opioids with complaints of sexual side effects, dehydroepiandrosterone is the first-line option. This is because adrenal gland suppression is a greater contributor to female androgen deficiency. In younger women, oral contraceptives with a relatively androgenic progestin component may be used [121; 123].

ACETAMINOPHEN TOXICITY

Several codeine, hydrocodone, and oxycodone formulations include acetaminophen. In the United States, acetaminophen toxicity has replaced viral hepatitis as the most common cause of acute liver failure and is the second most common cause of liver failure requiring transplantation [227]. In 2009, the FDA imposed a daily dose ceiling for acetaminophen of 4,000 mg; however, doses less than 4,000 mg per day can produce subclinical liver toxicity. Concurrent alcohol use also increases the risk, and chronic alcohol use is a high risk factor for fatal acetaminophen toxicity [222; 225]. It is crucial to use caution when prescribing any opioid preparation containing acetaminophen to older patients or patients with hepatic or renal disease.

OPIOID USE DISORDERS

There is no adequately validated instrument to differentiate pain patients who are at risk of dependence from those who are not. Research suggests that patients, even alcoholics, with no history of opioid dependence are not at heightened risk of becoming addicted with short-term opioid exposure. However, those with a positive history of dependence would benefit from active recovery efforts while receiving such medications.

Despite the rise in prescription opioid analgesic use and misuse, definitive data on the rate of dependence among patients administered opioids for acute pain does not yet exist. There is, however, agreement on how to minimize the risk of iatrogenic dependence. These steps include screening for risk potential based on a family history of substance abuse and the exploration of different delivery systems that adequately treat pain but minimize abuse potential. Although a pattern of aberrant behavior may be grounds for caution, a history of opioid misuse does not necessarily preclude a patient from successful treatment with an opioid. Screening for psychologic disorders is also advisable, including psychosomatic causes of pain.

CONCLUSION

Safety is the foundation of effective pain control with opioid prescribing. Safety risks are mitigated by understanding that most opioid analgesic overdoses involve co-ingested CNS sedatives or alcohol, with side effects, tolerability and analgesic response largely determined by comorbidities, drug interactions, and genetic variation.

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