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Full Opioid Agonists and Tramadol: Pharmacological and Clinical Considerations

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Abstract

Opioids are mu receptor agonists and have been an important part of pain treatment for thousands of years. In order to use these drugs appropriately and successfully in patients, whether to control pain, to treat opiate-induced side effects, or opiate withdrawal syndromes, a solid understanding of the pharmacology of such drugs is crucial. The most recognized full agonist opioids are heroin, morphine, codeine, oxycodone, meperidine, and fentanyl. Phenanthrenes refer to a naturally occurring plant-based compound that includes three or more fused rings. The opioids derived from the opium plant are phenanthrene derivatives, whereas most synthetic opioids are simpler molecules that do not have multiple rings. Methadone acts as a synthetic opioid analgesic similar to morphine in both quality and quantity; however, methadone lasts longer and in oral form, has higher efficacy, and is considered a diphenylheptane. Fentanyl is a strong synthetic phenylpiperdine derivative that exhibits activity as a mu-selective opioid agonist approximately 50 to 100 times more potent than morphine. Meperidine is another medication which is a phenylpiperdine. Tramadol is considered a mixed-mechanism opioid drug, as it is a centrally acting analgesic that exerts its effects via binding mu receptors and blocking the reuptake of monoamines. Some of the most common adverse effects shared among all opioids are nausea, vomiting, pruritus, addiction, respiratory depression, constipation, sphincter of Oddi spasm, and miosis (except in the case of meperidine). Chronic opioid usage has also established a relationship to opioid-induced hypogonadism and adrenal suppression. Physicians must be stewards of opioid use and use opioids only when necessary.

Keywords: Opioids, Full Agonists, Tramadol, Methadone, Meperidine, Fentanyl

1. Context

Opioids are mu receptor agonists and have been an important part of pain treatment for thousands of years. In order to use these drugs appropriately and successfully in patients, whether to control pain, to treat opiate-induced side effects, or opiate withdrawal syndrome, a solid understanding of the pharmacology of such drugs is crucial (1). Some specific pharmacokinetic characteristics, such as half-life, clearance, and volume of distribution, of these drugs have been well-understood for many years. However, metabolism and the role of metabolites in the pharmacodynamic response in patients remains less clearly understood (2).

Opioids activate specific transmembrane receptors that are expressed by both central and peripheral neurons, as well as by neuroendocrine, immune, and ectodermal cells. The three main types of opioid receptors in the central nervous system are mu, delta, and kappa. These receptors are classified within the class A gamma subgroup of seven transmembrane G protein-coupled receptors (GPCRs) (3). Opioids activate these specific receptors that couple G proteins, which go on to initiate intracellular communication and activate the process of signal

transduction (4). Activation of mu-opioid receptors in the CNS results in respiratory depression, analgesia, euphoria, and miosis. Alternatively, the stimulation of peripheral mu-opioid receptors, such as those in the smooth muscle of the gastrointestinal and respiratory tracts, results in cough suppression and opioid-induced constipation (5).

Opioid drugs act by binding to specific receptor sites in the brain (6). These sites also happen to be the binding sites of endogenous opioid-like peptides that produce similar effects, including the prototypic opioid effects of reward, withdrawal, and analgesia, via actions at those very receptors (7). These three opioid systems were found to be encoded by individual genes for pre-proenkephalin, pre-proopiomelanocortin, and pre-prodynorphin. Each of these genes will code for peptides that bind to mu (MOR), kappa (KOR), and delta (DOR) receptors, respectively. The discovery of these endogenous peptides and their receptors confirmed that opioid drugs act by mimicking these endogenous opioid systems. MOR is the main target for opioid analgesics, but DOR and KOR also regulate pain and analgesia (6). Specifically, mu receptor activation can mediate a variety of G proteins that affect messenger-generating enzymes, like adenyl cyclase and phospholipase C. Acutely, opioids can decrease secondary messengers like cyclic adenosine monophosphate (cAMP), while chronic opioid receptor activation has the opposite effect to acute administration, and results in up-regulation of cAMP (5).

2. Full Opioid Agonists- Phenanthrenes

Phenanthrenes refer to a naturally occurring plant-based compound that include three or more fused rings. The opioids derived from the opium plant are phenanthrene derivatives, whereas most synthetic opioids are simpler molecules that do not have multiple rings (8). The prototypic phenanthrene derivatives that serve as full agonists to the mu receptor include morphine, hydromorphone, and oxymorphone. Heroin (diamorphine, diacetylmorphine) is a strong agonist. Codeine, dihydrocodeine, hydrocodone, and oxycodone are mild to moderate agonists. Some phenanthrenes have mixed receptor actions, and great care should be taken in prescribing these drugs with pure agonists because of the unpredictability of analgesic effects and precipitation of explosive abstinence syndrome. Nalbuphine is a strong K-receptor agonist and a Mu-receptor antagonist, which causes respiratory depression at higher doses that is not reversed with naloxone (9, 10). Buprenorphine is a long-acting phenanthrene derivative that is a partial Mu-receptor agonist and a K-receptor antagonist, which is FDA-approved for the management of opioid dependence (11). In contrast to methadone, high-dose administration of buprenorphine results in Mu-opioid antagonist actions. Suboxone is a combination of Buprenorphine with Naloxone, a Mu-receptor antagonist, to prevent illicit intravenous use. Sedation occurs more frequently with opioids closely related to the phenanthrene molecule, whereas synthetic agents, such as meperidine and fentanyl, have fewer sedative effects (8).

One phenanthrene, halofantrine hydrochloride, is effective against erythrocytic (but not other) stages of all four human malaria species (8). Despite being approved by the FDA, it is not available in the US but is widely available in malaria-endemic countries.

3. Full Opioid Agonists- Diphenylheptanes

By the late nineteenth century, opium derivatives, including laudanum and morphine, were widely used as a treatment for chronic pain to the extent that different populations, including civil war soldiers, physicians, and housewives, became addicted (12). The Harrison Act of 1914 was passed to prohibit maintenance treatment for opiate addiction and lead to a massive surge in heroin use on the streets. By 1920, addiction had become recognized, but it wouldn't be until the 1960s that the scientific community began to realize that a maintenance program for addicted individuals was necessary. During WWII, morphine supplies were controlled by allied forces in the east, and so German scientists began attempts to synthesize a compound similar, which lead to the birth of methadone (12). By 1947, methadone would be known as *dolophine* (or *dollies* on the streets), coming from the word *dolor* (pain) and *fin* (end) (13). In the 1960s, Dole and Nyswander published a study at the Rockefeller Institute advocating for the use of methadone to treat heroin withdrawal, and this instigated the change for methadone to replace morphine as the treatment for heroin addiction (14).

Methadone acts as a synthetic opioid analgesic similar to morphine in both quality and quantity; however, methadone lasts longer and in oral form has a higher efficacy (15). Methadone is synthesized through the alkylation of diphenyl acetonitrile by sodium amide and 1-dimethylamino-2-propyl chloride. The result is combined with ethyl magnesium bromide and subsequently hydrolyzed into the racemic mixture of methadone or 4,4-diphenyl-6-dimethylaminoheptan3-one (15). Due to the presence of an asymmetric carbon atom, methadone has two enantiomeric forms, d and l isomers. The l isomer is the component that has analgesic effects and has been found to have twice the analgesic potency of morphine (16). Once thought to be completely inactive, recent studies have shown that the d isomer has NMDA receptor antagonist activity and may play a part in morphine tolerance

(17). This activity at the NMDA receptor makes methadone more effective in treating neuropathic pain than the other opioids (18). Methadone is available in the United States only as a racemic mixture of both enantiomers (19).

Methadone is lipophilic and absorbed rapidly after oral administration with an oral bioavailability of 60 - 80% (17, 18). The plasma half-life is approximately twenty-four hours but is variable from 5 to 130 hours which explains why it is difficult to predict peak plasma levels and accounts for the large variability in pharmacokinetics amongst patients (17, 19). Methadone can be detected in the blood about 15-45 minutes after oral administration (20). Methadone is bound to plasma proteins such as α1-acid glycoprotein, which are increased in stressful conditions such as heroin addiction; thus, there is a rise in protein-bound methadone and a decrease in free methadone (18). In addition, methadone is also bound and distributed to the liver, lung, and adipose tissue, which accounts for the long plasma half-life. Methadone takes several days to have its full effect due to tissue saturation which explains why some users often feel they don't have enough methadone on board in the first few days of treatment (13). Studies have shown that patients on methadone are usually maintained on 80-120mg oral methadone daily, which is considered a high dose, and 20-60mg, which is considered low dose (16). Patients are usually started at an initial dose of 10-30 mg and can be increased gradually over the first to three weeks (21). Methadone is primarily metabolized by the liver through demethylation by CYP3A4 in addition to numerous other cytochromes (22). There is great variability in terms of pharmacokinetic properties, which has made it difficult to make dosing guidelines (23).

Due to the extensive metabolism by the cytochrome system and the overall lengthy nature of methadone maintenance treatment, methadone carries a risk of interacting with other drugs. Antidepressants, anticonvulsants, benzodiazepines, macrolides, antifungals, and antiretrovirals have been shown to interact with methadone. It is important to note the metabolic inducers of CYP3A4, which causes an increase in enzyme activity and a decrease in the amount of methadone readily available. This may lead to withdrawal symptoms making it imperative that careful observation of the patient is done to ensure proper dosage. It has been shown that chronic alcohol use causes an increase in the CYP3A4 system, thus decreasing free methadone available (18). Thus far, the relationship between dose, plasma level, and effect has not been fully understood and yields further investigation (22).

3.1. Clinical Use of Methadone

In 2007, the United States lost $55.7 billion dollars related to prescription opioid abuse (14). Methadone is an effective choice in keeping people in long-term treatment for opiate addiction. Methadone maintenance treatment is associated with overall increased patient productivity and decreased risk of relapse due to methadone's ability to block the euphoric effects of heroin. The long half-life allows for a decrease in overall withdrawal symptoms and in comparison to other opioid agonists, it produces less euphoria and thus less reinforcement. Research has shown that methadone maintenance treatment is also associated with decreased criminal activity and the ability of drug users to switch from intravenous to parental use, thus reducing the risk of HIV (14). Methadone treatment actually increased with the discovery of HIV in efforts to prevent the spread of AIDS (13). Methadone has also been shown to effectively reduce chronic pain conditions such as cancer pain (24).

Of particular interest, doses of 60-120 mg of methadone per day are associated with higher rates of success due to the fact that heroin has been found to be purer today than in the past (12). Methadone differs from the other opioid agonists in several ways. Methadone's actions are more prolonged, and the onset of withdrawal symptoms is less intense but more prolonged than the others. Methadone also effectively hinders the euphoric effects of other drugs like morphine and helps to stop cravings in order to prevent relapse (16).

3.2. Side Effects of Methadone

Methadone acts primarily through the mu receptor and thus is responsible for the euphoria and analgesic effects of methadone; in addition, mu receptor agonists are associated with constipation and respiratory depression (14). Studies have shown that in comparison to buprenorphine, methadone is more likely to cause respiratory depression (14). Methadone has been found to be twice as powerful as an analgesic than morphine; therefore, it is important to monitor opiate-naïve patients for respiratory depression and overdose (16). Tapering off methadone must be done slowly to avoid withdrawal symptoms such as insomnia, nausea, mood changes, diaphoresis, and muscle cramps (18). Risks involved in the use of methadone include QT prolongation (25). This can put the patient at risk for a fatal arrhythmia called torsades de pointes. Caution should be used when methadone is used with other medications that could prolong the QT interval. These could be macrolide antibiotics, non-sedating antihistamines, some antipsychotics, and some antidepressants (25).

4. Full Opioid Agonists- Phenylpiperdines

4.1. Fentanyl

Fentanyl is a strong synthetic phenylpiperdine derivative that exhibits activity as a mu-selective opioid agonist, approximately 50 to 100 times more potent than morphine (26, 27). It is one of the most commonly used opioid analgesics in modern anesthesia and pain therapy (28, 29). Fentanyl had a relatively slow take-off after FDA approval and only precipitously increased in popularity after the concept of high-dose opioid anesthesia for critically ill patients undergoing open-heart surgery, and vascular surgery was introduced (26). After trials of using morphine for this technique resulted in patients with a large adverse effect profile, high-dose fentanyl/oxygen was studied and found to be superior to morphine (26). Several other routes of delivery of the drug continue to be studied, and for now, it continues to be one of the most popular drugs in the perioperative periods (30-32).

4.2. Fentanyl Analogs: Structure-Activity-Relationship Study

Opioids can be classified into groups based on their chemical structure. Fentanyl is the prototype for the 4-anilodopiperdine, a highly potent class of synthetic opioid analgesics (33). Today, structure-activity relationships (SAR) are the primary driver in drug discovery and optimization (34). Substitution of fentanyl analogs for methyl groups in the three-position of the piperidine ring severely decreased potency from fentanyl. This change suggests that the potency of the 4-anilodopiperdine class is more strongly related to steric factors of bulk and cis/trans isomerism than polarity or chemical reactivity (33). Additionally, three-position substitution effects on neurotoxicity paralleled that of potency and duration of action, suggesting that there may be similar receptors responsible for the anti-nociceptive and neurotoxic effects of opioids (33).

4.3. Fentanyl Formulations in the Management of Pain: An Update

Initially primarily designated for the intraoperative anesthesia setting, fentanyl has increasing versatility in use and route of administration (27). Fentanyl possesses high lipophilicity, crucial to its faster onset and potency (27). Parenteral formulations of the drug posed limitations to the setting of administration and a higher risk of complications, resulting in a push to develop non-parenteral formulations (27). The first of these was a transdermal patch that proved successful for achieving adequate and steady analgesia for cancer patients (27, 32). Buccal/transmucosal administration, while not as frequently used, was found to be superior to immediate-release morphine for transient breakthrough pain for cancer patients (27). Transpulmonary inhaled fentanyl is continuing to be studied as a potential novel route of administration (27). Overall, these newer formulations have expanded the versatility of fentanyl from the peri-operative period to indications in the management of chronic and breakthrough pain in multiple care settings (27).

4.4. Intrathecal Meperidine

Meperidine is another medication which is a phenylpiperdine. Intrathecal meperidine is able to provide analgesia and nerve conduction block at the proximal dorsal root in a fashion irreversible to naloxone administration (35). It provides analgesia for about six hours and minimally spreads rostrally when compared to intrathecal morphine (36). Therefore, delayed respiratory depression is a rarer complication with intrathecal meperidine versus morphine (37). At higher doses, intrathecal meperidine is associated with reactions such as severe pruritus, nausea, and sedation. Furthermore, anaphylaxis was reported by meperidine (38).

5. Opioid Agonist Uses

The foremost applications of opioid agonists are analgesia and anesthesia. Acute courses of opioid medications are considered appropriate for the management of surgical and acute traumatic pain, as well as for cancer-related pain and non-cancer pain that has failed non-opioid management (39). In the surgical context, the direct application of morphine to spinal structures can produce local surgical anesthesia while minimizing systemic side effects (40, 41). In chronic pain patients, pain management specialists may elect to implant a catheter for the programmed delivery of opioids to the epidural space (42). In the setting of persistent, unremitting cancer pain, the transdermal patches of fentanyl are efficacious (32). while lozenges of fentanyl citrate are effective for breakthrough cancer pain and buccal mucosal administration of fentanyl via transdermal patches and lozenges (43).

Opioid agonists are unique in their ability to simultaneously treat the emotional and physical components of pain. Full or partial opioid agonists demonstrate activity primarily at the opioid receptor mu (), with variable activity at the of the opioid-like subtype-1(OR-1) receptors delta (δ) and kappa (κ), mimicking the activity of endogenous endorphins and enkephalins to produce analgesia by activating inhibitory G-protein coupled receptors that modulate neurotransmission primarily in the brain, spinal cord, and also at some sites in the periphery. Within the brain, opioids bind to neurons that mediate nociception in the locus coeruleus, rostral ventral medulla, and periaqueductal gray matter (43).

The current opioid crisis requires physicians to carefully consider the contexts in which specific opioid pain medications will meet the clinical needs of specific patients (39). Opioids are generally not useful in the treatment of nociceptive pain, neuropathic pain, functional pain, migraine headache pain, or widespread soft tissue pain. Thus, the first role of the physician is to educate the patient about whether opioids are an effective means of reaching their pain management goals for a specific pain problem (44).

The effective dosing of opioid medication for analgesia is partially dependent upon psychological variables, including baseline anxiety, pain sensitivity, and pain chronicity. Additional somatic sources of variability include nicotine exposure, pulmonary function, and hepato-renal function. The interaction between these variables necessitates circumspect dosing practices (39).

Expectation management is important in analgesic opioid therapy. The physician should communicate the goal of outpatient opioid therapy as pain reduction and relatively improved functionality, as opposed to the complete absence of pain (39). Also, it is important to educate patients that poor responders to low or medium doses are better served by alternative mechanisms of analgesia rather than higher doses of opioid medication (39).

In addition to their analgesic effects, opioids exert a multitude of systemic effects. While many of these effects are viewed as undesirable and recommend local applications when possible, some of these effects are exploited for clinical benefits. These include:

(1) Cough Suppression: Opioid agonists are centrally-acting suppressors of the cough reflex. Codeine is the opiate of choice for suppression of chronic pathologic cough due to its favorable profile of systemic side effects. However, chronic suppression of cough creates a liability for secretion accumulation, leading to atelectasis or airway obstruction (43).

(2) Anti-Diarrheal: Opioid agonists are generally effective in controlling diarrhea that is not associated with an infection. Synthetic opioids like loperamide and diphenoxylate are now preferred for anti-diarrheal applications due to their minimal effects upon the central nervous system (43).

(3) Myocardial Ischemia with Pulmonary Edema: For patients with painful myocardial ischemia that is accompanied by pulmonary edema, morphine is a common physician choice for the management of STEMI in the absence of comorbid respiratory depression (43). Murine in vivo models have demonstrated the capacity of morphine to reduce reperfusion injury by reducing the overall oxygen demand of heart tissue. There is currently insufficient data to determine that these findings are applicable to humans (45). However, a 2019 meta-analysis of randomized controlled trials demonstrated that the use of morphine for acute coronary syndromes resulted in increased in-hospital mortality. The authors of the metanalysis expressed high confidence that morphine decreases the antiplatelet effect of P2Y12 inhibitors, suggesting a potential mechanism for the observed increase in mortality.

(4) Mitigation of Amphotericin-B-induced shivering: Amphotericin B is an infusion-administered antifungal therapy that is sometimes required in the treatment of opportunistic fungal infections that inoculate immunosuppressed cancer patients. Shivering often accompanies the administration of amphotericin-B, and these side effects are significantly deleterious to the quality of life in these patients. The administration of the opioid meperidine has proven effective in the mitigation of these side effects (46). Although all opioids have some propensity to mitigate shivering, this property is most pronounced in meperidine (43).

6. Atypical Opioids

Tramadol is considered a mixed-mechanism opioid drug, as it is a centrally acting analgesic that exerts its effects via binding mu receptors and blocking the reuptake of monoamines (serotonin and norepinephrine). Tramadol, along with its active metabolite (M1), inhibits ascending pain pathways by binding to mu opiate receptors in the central nervous system, leading to an altered perception of and response to pain. Tramadol and M1 also inhibit the reuptake of serotonin and norepinephrine, both components of the descending inhibitory pain pathway responsible for pain relief (47, 48).

Tramadol's unique inhibitory mechanism of blocking the reuptake of monoamines, like serotonin and norepinephrine, leads to a risk of side effects associated with increased monoamine availability. Two of these side effects are serotonin syndrome and seizures. These are not so prevalent in the general population but can be extremely dangerous when left unrecognized or untreated (49). Elevated risk of serotonin syndrome and seizures is present in patients with medical comorbidities, use or abuse of supra-therapeutic doses of tramadol, or simultaneous administration of pro-convulsant serotonergic cytochrome P-450 inhibitors. Patients who are rapid cytochrome P-450 2D6 metabolizers experience a stronger tramadol opioid response and are at an increased risk for abusing or overdosing with tramadol. Thus, clinicians are encouraged to consider utilizing pharmacogenetic testing to predict an individual's response, risk of addiction, and thus the risk of developing serotonin syndrome or seizures. Serotonin syndrome and seizures as a result of tramadol ad-

ministration can both be treated effectively with benzodiazepines, supportive care, and discontinuation of tramadol and other contributing agents (50).

Tramadol's special pharmacological characteristics provide not only special adverse effects but also provide unique benefits, as well. As tramadol has a milder action on opioid receptors as opposed to typical opioid drugs, the side effects of tramadol administration are also less significant than those of classic opioids. This means that with tramadol administration, there is a less significant risk of respiratory depression and constipation, as well as a lower risk of tolerance and dependence on the drug. In addition, the analgesic efficacy of tramadol has been proven extensively in animal models in the context of both acute and chronic pain (51).

For many years, tramadol has been used as a well-tolerated alternative to other drugs used in moderate pain relief related to its "mixed mechanism" opioidergic and monoaminergic activities. However, in recent years, studies show that there might be other mechanisms involved in its activity and that it can be used in a variety of ways in pain management. Tramadol has the ability to modulate various mediators involved in the pain signaling pathway, as well as modify the communication between neuronal and non-neuronal cells at various sites. Thus, tramadol has the potential to modulate both peripheral and central neuronal hyper-excitability. Because the drug has such a wide range of molecular targets, it is able to contribute to pain relief in numerous ways. Tramadol can be used to target pain post-operatively, low back and neuropathic pain, and pain associated with labor, osteoarthritis, fibromyalgia, and cancer (52). Tramadol typically provides a stronger and frequently safer alternative to treating pain with high doses of NSAIDs or low doses of stronger opioid medications. Due to its monoaminergic effects, tramadol is also capable of anxiolytic, antidepressant, and anti-shivering activities that can potentially improve pain management outcomes (52).

7. Full Opioid Agonist Concerns

7.1. Individual Side Effects

Full mu-receptor agonist opioids are some of the most prescribed medications due to their extreme effectiveness as a pain analgesic (53). but they often come with common side effects. The most recognized full agonist opioids are heroin, morphine, codeine, oxycodone, meperidine, and fentanyl. The list is long and expanding, as new metabolites are frequently synthesized to evade law enforcement and for enhanced potency and efficacy (54). Some of the most common adverse effects shared among all opioids are nausea, vomiting, pruritus, addiction, respiratory depression, constipation, sphincter of Oddi spasm, and miosis (except in the case of meperidine). Full opioid agonists tend to have more severe side effects, and severe misuse of full opioid agonists may result in coma and death from respiratory depression.

Opioid mismanagement frequently results in long-term opioid use in acute pain settings, which comes with its own unique side effects. Preclinical studies have suggested that chronic morphine use may suppress immune system responses, and observational studies have shown an association between long-term opioid usage and infection risk (55). However, clinical trials remain inconsistent, and direct causation has not yet been established. Chronic opioid usage has also established a clear relationship to opioid-induced hypogonadism and adrenal suppression (56). Long-term opioid users have been reported to have poorer outcomes during surgical procedures due to being prone to injuries, and one proposed theory is that the adrenal suppression blunted the usual stress response during acute illness (57-59). In the surgical setting, chronic preoperative opioid use is associated with increased postoperative complications, including infection, poorer outcomes after surgery, longer hospital stays, and higher health care costs (60). Lastly, chronic opioid usage also leads to individuals reporting higher pain upon cessation of opioids. Chronic opioid use impacts more than just the patient, as the public has to suffer from increased healthcare costs and the effect that both prescribed and illicit opioid use has on society.

7.2. Social Side Effects

Full Opioid drugs are known to be very dangerous, with high abuse potential and severe adverse effects, including coma and death. For the last five decades, there has been a dramatic rise in opioid use in the developed world, which peaked between 2011 and 2013, and it continues to remain high (53). As opioid prescription and use have risen, so too have the related mortality and complications of opioid use. There was almost a threefold increase in opioid deaths in the last two decades (61). Opioid prescriptions have led to opioid addictions, which are met by illicit opioid usage that can lead to death. Often street heroin is laced with other opioid metabolites, sometimes unknown to the users; the most notorious drug being fentanyl. Illicit fentanyl and its analogs are a highly dangerous threat to public health because contact with minuscule doses can result in lethal exposure. People unknowingly and unwillingly consume laced products that lead to opioid intoxication and death (54).

Opioid usage targets minorities in particular. While the overall opioid dispensing rate in 2019 was 46.7 pre-

scriptions per 100 people, some counties had rates that were six times higher than that; and in 5% of U.S. counties, enough opioid prescriptions were dispensed for every person to have one (53). The problems with opioid effects some places in the United States worse than others, particularly minority-heavy places. Deaths by opiates disproportionately affect the Black and Hispanic communities. The rate of increase of Black opioid overdose grew by 40% between 2015-2016, whereas the overall population increased by 21% (62). In 2017, the CDC YRBS reported that high school Hispanic youth had the highest prevalence of select illicit drug use and prescription opioid misuse compared to the total high school youth population and other race/ethnicities (63).

8. Clinical Studies: Safety and Efficacy

Morphine remains the standard for analgesia against which all strong analgesics are compared (43). The pharmacokinetics and metabolism of various natural opiates and synthetic opioids are diverse, lending a wide range of properties that make each drug more or less appropriate for specific applications. Since physicians and the general public have become aware of the widespread epidemic of opioid abuse in the United States, the increasingly circumspect prescription of these medications drives interest in achieving anesthesia or analgesia with the minimum usage of opioid medications (43).

Patients treated with morphine with diminishing analgesic response can often exhibit similarly diminished analgesia and diminished systemic side effects, the "cross-tolerance phenomenon." However, clinical experience has shown that because such cross-tolerance is often incomplete among mu receptor agonists, the rotation of a patient to another opioid agonist achieves a clinically significant improvement of analgesia (43). This is a superior alternative to incrementally increasing opioid dosages to compensate for tolerance.

8.1. Effects of Maternal Opioid Use Upon the Neonate

Although physicians in the United States have been aware of neonatal withdrawal syndromes since the 1870s, physicians continue to prescribe opioid medications for common pregnancy-related pain complaints, including lower back pain, pelvic pain, myalgias, and migraine headaches. In the 1960s, the advent of methadone maintenance therapy in pregnant women addicted to heroin led to decreased fetal mortality and increased birthweights. However, it was noted that fetuses exposed to methadone maintenance therapy experienced more pronounced withdrawal symptoms than fetuses exposed only to heroin. The relatively recent advent of maternal buprenorphine maintenance therapy uses a partial mu agonist in place of a full mu agonist (e.g., methadone) to bind mu receptors with decreased activity but increased affinity. Additionally, whereas methadone is typically prescribed in the setting observed clinical dosing, buprenorphine can be taken by the outpatient at home. It should be noted that fetuses born to mothers on methadone and buprenorphine maintenance therapies continue to have significantly lower birth weights, in the 10%ile of standard population growth curves. Although multiple studies have examined the possibility of increased odds ratios of specific birth defects in these children, and there is some evidence of increased incidence of congenital heart defects, neural tube defects, and clubfeet, these studies have lacked the requisite statistical power to conclude that the small numbers of observed birth defects were conclusively related to opioid exposure (64).

8.2. Examining Prevalence of Opioid-Induced Hypogonadism in Males

Previous small studies suggested that the chronic use of opiates in males led to the development of hypogonadism in up to 90% of patients due to Increased testosterone secretion and HPA axis suppression. However, a 2019 retrospective cohort study of 53,888 men taking opioids for a period of 90 days or longer were matched to controls who took opioids for 14 days or less. 9.44% of the experimental group carried a hypogonadism diagnosis after five years, and 4.85% were recipients of testosterone therapy for the treatment of hypogonadism. These results are clinically significant, and clinicians should be alert to the possible need for testosterone monitoring male patients prescribed prolonged opioid therapy. However, the prevalence of hypogonadism in this population was much lower than was previously suggested by earlier, small-scale studies that suggested an incidence rate as high as 90% (65).

9. Evidence-Based Challenges to Physicians' Conventional Assumptions About Opioids

9.1. Conventional Assumptions About Relative Efficacy

In addition to simply reducing physician reliance upon opiates for short-term analgesia, studies are currently re-examining the means and methods for the delivery of analgesia in common medical procedures. One significant area of inquiry is the delivery of analgesia during caesarian section. In 2020, Sharpe et al. examined the efficacy of hydromorphone as a replacement for morphine, which has long been considered the gold standard of intrathecal analgesia for caesarian section. The study

showed no difference in the analgesia produced by hydromorphone and that of morphine. Although hydromorphone also carries significant addiction potential, the result confounded researchers' expectation that morphine would produce better anesthesia (66). Although it does not directly compare morphine to a non-opioid drug, this study is likely to invite further inquiries testing long-held assumptions about the applications of opioids to surgical pain. Additionally, hydromorphone carries a lower burden of subjective drowsiness and produces more rapid postoperative recovery (67).

9.2. Conventional Assumptions About Secondary Indications

Shortly after the introduction of the opioid meperidine in Latin America, Calderyo-Barcia described an association between meperidine and uterine contractility. As a result, meperidine has historically been used in Latin American hospitals for an indication of dystocia. A 23-month randomized controlled trial published in 2004 by Sosa et al. demonstrated that there was no difference in the mean labor times of patients with dysotcia who received meperidine and those who did not. As a result, the study concluded that dystocia was an inappropriate indication for meperidine (68).

10. Replacing Common Applications of Acute Opioid Therapy with Non-opioid Alternatives

The most direct means of reducing the prevalence of opioid addiction is to objectively revisit the efficacy of non-opioid medication versus opioids in settings where opioid medications may be considered appropriate. A 2017 randomized controlled trial examined outcomes of 416 patients presenting to emergency rooms for moderate-to-severe acute extremity pain that warranted radiography. Chang et al. compared the efficacy of 400 mg of ibuprofen and 1000 mg of acetaminophen versus equipotent combinations of oxycodone, hydrocodone, or codeine, each with an appropriate dose of acetaminophen. The study concluded that there was no significant difference between any of the studied combinations, suggesting that the combination of 400 mg ibuprofen and 1000 mg acetaminophen is a reasonable substitute for common acute ER pain complaints (69).

11. Examining Localized Applications of Opioids

The effort to achieve greater analgesia with lower doses of opioids extends to experimentation with more localized applications of opiate anesthetics.

11.1. Epidural Versus Intravenous Administration of Meperidine

As early as 1994, Paech, et al. demonstrated that the route of delivery of opiate medication could reduce overall exposure to opioid painkillers. This study presented a variation on patient-controlled anesthesia in which the opioid meperidine was delivered epidurally instead of intravenously. Patients receiving the epidural administration required a significantly lower doses of meperidine than those receiving intravenous administration (67).

Other longstanding studies have demonstrated that following epidural administration, the more concentrated availability of the active meperidine metabolite normeperidine creates a greater liability of off-target CNS toxicity, such as seizures, tremors, myoclonus hyperreflexia, and agitation. However, when identified, these side effects are reversible within 1-2 days with supportive therapy and benzodiazepine administration (Table 1) (70).

12. Conclusions

In the setting of the current opioid crisis, the addictive potential of opiates is being reconciled after many decades of overuse. Fortunately, with the advent of evidence-based medicine, increasing data availability through electronic records and billing management systems and the increasing availability of precise tools of molecular biology, physicians are well positioned to reevaluate conventional indications for specific opioids. Additionally, these tools allow physicians to test new opioid and non-opioid applications, as well as novel routes of administration to achieve superior analgesia while lessening the burdens of systemic side effects and the liabilities for dependence and addiction. Where terminal cancer and other chronic pain conditions warrant continuous opioid therapy for severe pain, novel protocols for the rotational use of opioid therapies and their non-opioid adjuvants can maintain higher analgesic efficacy over longer periods of time.

Current procedural practice allows physicians to apply opioids over increasingly narrow and targeted distributions. In the future, it is foreseeable that the advancement of cellular and molecular techniques may overcome the perennial problems of dependence, addiction and tolerance, as physicians gain the ability to manipulate the prevalence of specific cellular receptors. Likewise, manipulation of these receptors holds promise for limiting the diverse systemic off-target effects in patients requiring chronic opioid therapy. Physicians must be stewards of opioid use and use opioids only when necessary.

Table 1. Studied Resources

Author (y)	Groups Studied and Intervention	Results and Findings	Conclusions
Machado et al. (2019) (71)	A meta-analysis of 13 double-blinded, controlled trials.	Measures of pain scores, postoperative opioid consumption, and patient satisfaction favor the use of intraoperative methadone over other opioids. The incidence of opioid-related side effects was not increased by opioid use.	Intraoperative methadone is effective in reducing postoperative pain scores, reducing postoperative opioid consumption, and increasing patient satisfaction.
Sharpe et al. (2020) (66)	Single-center, double-blinded randomized controlled trial of 138 patients undergoing Caesarian section	No significant difference in pain scores with movement at 24 hours post-surgery between equipotent doses of intrathecal morphine and intrathecal hydromorphone.	Both intrathecal morphine and intrathecal hydromorphone provide effective post-cesarean analgesia when combined with a multimodal analgesia regimen. This is significant because hydromorphone is generally characterized by a less onerous side-effect profile.
Paech et al. (1994) (67)	Randomized, double-blind cross-over study was conducted for 24 hours following caesarian section in 48 patients.	Significantly lower pain scores at rest and when coughing for patients receiving patient-controlled meperidine analgesia via an epidural route versus an intravenous route. Patients receiving epidural meperidine used 50% less than patients assigned to the intravenous control. Satisfaction scores significantly favored the epidural route.	Patient controlled epidural analgesia with meperidine produces high-quality analgesia with significantly lower dose requirements in the first 24 hours post caesarian section versus intravenous route.
Chang et al. (2017) (69)	A total 416 patients presenting to an emergency room with an extremity injury necessitating radiographs were divided into one experimental and three control of four treatment groups. The experimental group received 400 mg of ibuprofen and 1000 mg of acetaminophen. The three control groups received a combination of an opioid and acetaminophen.	At two hours after treatment, the patients in the nonopioid experimental group experienced analgesia at least equal to that of the patients in each of the opioid control groups.	Effective analgesia can be achieved in many emergency presentations for moderate-to severe musculoskeletal extremity injuries without the use of opioid medications, suggesting that opioid prescribing in the emergency room for these acute injuries can be significantly reduced in the future.
Baillargeon et al. (2019) (65)	A review of CPT codes for 55,888 male patients who had taken opioids for more than fourteen days was compared to a control cohort of 55,888 men who had taken opioids for fewer than 14 days. Patients were screened for three events: Serum testosterone screening, diagnosis of hypogonadism, and receipt of exogenous testosterone therapy.	17.15% of patients were screened for low testosterone within 5 years. 9.44% of received a diagnosis of hypogonadism. 5.44% of patients received exogenous testosterone therapy.	Although this study confirms a relationship between the long-term use of opioid medication and hypogonadism in male patients, the actual incidence of hypogonadism is dramatically lower than was previously suggested by small-scale studies that purported to show an incidence as high as 90%. Therefore, physicians should be aware that hypogonadism is a potential complication of opioid therapy and should monitor testosterone levels periodically in chronic opioid users.
Sosa et al. (2004) (68)	Four-hundred and seven pregnant women admitted in labor to the public obstetric service at Pereira Roussal Hospital in Montevideo, Uruguay over 23 months. Dystocia of labor was defined as a mother who required any active management of labor to improve uterine contractility. For the experimental group, meperidine was administered during the second stage of labor.	There was no difference in the mean duration of labor between the experimental group that received meperidine and the control group that did not.	Contrary to the conclusions of Latin American physicians in the 1950s, meperidine does not improve uterine contractility and should no longer be indicated for this obstetric purpose.

Footnotes

Authors' Contribution: Study concept and design: AEN, LAK, SK, MP, EMC, AMK, ADK; Analysis and interpretation of data: AEN, MP ES CDC; Drafting of the manuscript: LAK, SK, CDC, FI, OMM, EMC; Critical revision of the manuscript for important intellectual content: AEN, LAK, SK, MP, EMC, FI, OMM, AMK, ADK; Statistical analysis: AEN, LAK, SK, MP, ES, CDC.

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