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Opioids today: From pharmacology to crisis management and emerging solutions

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Abstract

Background: Opioids are a critical component in managing moderate to severe pain, especially in conditions like cancer and post-surgical recovery. However, their use is accompanied by significant risks, including tolerance, dependence, and addiction, which have contributed to a global opioid crisis. The need for safer pain management strategies and regulatory measures has never been more pressing.

Main body: This review provides a comprehensive overview of opioid pharmacology, focusing on the most commonly prescribed opioids and their mechanisms of action. The clinical significance of various routes of administration is examined, highlighting their impact on efficacy and potential for abuse. The ongoing opioid crisis is discussed in detail, tracing its origins to the late 1990s and examining the factors that have exacerbated the problem, including aggressive pharmaceutical marketing and inadequate regulation. Strategies to reduce opioid exposure and prevent new addictions are explored, with a focus on the role of FDA regulatory measures, including updated prescribing guidelines and the development of abuse-deterrent formulations. Recent advancements in opioid research are also highlighted, including the exploration of non-addictive opioids, biased agonism, and targeted drug delivery systems. These innovations offer promise in improving pain management while minimizing the risks associated with opioid use.

Conclusion: The opioid crisis underscores the urgent need for improved pain management practices and safer opioid therapies. Ongoing research and regulatory efforts are critical to addressing these challenges. By integrating recent advancements into clinical practice, we can better balance the need for effective pain relief with the imperative to reduce the risks of addiction and other adverse effects associated with opioid use.

Keywords: Opioids; Morphine; Fentanyl; Naloxone; Oliceridine

1. Introduction

Opioids are a class of drugs that include natural, synthetic, and semi-synthetic substances derived from the opium poppy or designed to mimic its effects. They are primarily used for their analgesic properties but have a high potential for abuse and addiction. Opioids are primarily prescribed for managing moderate to severe pain, particularly in conditions like cancer, post-surgical pain, and chronic non-cancer pain. They are also used in palliative care to improve the quality of life for patients with terminal illnesses.

In acute pain management, opioids are effective for short-term use in scenarios such as postoperative pain or acute injury. For chronic pain management, while opioids can be part of a comprehensive pain management plan, their long-term use is controversial due to risks of tolerance, dependence, and hyperalgesia (increased sensitivity to pain). Prolonged use can lead to physical dependence and addiction, characterized by compulsive drug seeking and use despite harmful consequences [1].

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One of the most severe risks is respiratory depression, which can lead to fatal overdose. Over time, patients may develop tolerance, requiring higher doses to achieve the same analgesic effect, which increases the risk of adverse effects [2]. Common side effects of opioid use include nausea, constipation, drowsiness, and confusion [3].

The aim of this review article is to provide a comprehensive overview of opioid pharmacology, including commonly prescribed opioids, routes of administration and their clinical significance, the opioid crisis, strategies to reduce exposure and prevent new addictions, regulatory measures by the FDA to mitigate opioid-related risks, and recent advancements in the field of opioid research.

1.1. Pharmacology of Opioids

Opioids exert their effects by binding to specific receptors in the brain, spinal cord, and other parts of the body. These receptors are classified into three main types: mu (μ), delta (δ), and kappa (κ). The activation of these receptors leads to various physiological responses, including analgesia, euphoria, respiratory depression, and sedation. Mu receptors are the primary targets for most clinically used opioids, and their activation results in pain relief, euphoria, respiratory depression, and physical dependence [4]. Delta receptors, though less understood, are believed to play a role in analgesia and mood regulation. Kappa receptors, on the other hand, produce analgesia, dysphoria, and hallucinations when activated [5]. Recent research highlights the complexity of opioid receptor interactions, including the role of biased agonism, where different ligands preferentially activate certain signaling pathways over others, potentially leading to analgesics with reduced adverse effects [6, 7].

1.2. Commonly Prescribed Opioids

The most commonly prescribed opioids are morphine, oxycodone, hydrocodone, fentanyl, methadone, tramadol, codeine, and buprenorphine [8]. Morphine is often used to manage severe pain, particularly in a hospital setting, such as post-surgical pain or cancer-related pain. It works by binding to opioid receptors in the brain and spinal cord, altering the perception of pain. Available in oral, intravenous (IV), intramuscular (IM), intrathecal (IT), and subcutaneous (SC) forms, morphine is versatile in its applications. Common side effects include drowsiness, constipation, nausea, and respiratory depression [9].

Oxycodone is used for moderate to severe pain, often prescribed post-surgery or for chronic pain conditions[10, 11]. Like morphine, oxycodone binds to opioid receptors to reduce pain signals. It is available in immediate-release (IR) and extended-release (ER) forms, as well as combination products with acetaminophen (e.g., Percocet). Side effects include nausea, dizziness, constipation, and potential for dependence and abuse. Hydrocodone is prescribed for moderate to severe pain and sometimes for cough suppression. It works by binding opioid receptors in the brain and spinal cord. Commonly found in combination with acetaminophen (e.g., Vicodin) and in syrup form for cough relief, hydrocodone is widely used [12]. Side effects include nausea, vomiting, constipation, and risk of addiction.

Fentanyl is an extremely potent opioid used for severe pain, often in cancer patients or as part of anesthesia. It binds strongly to opioid receptors, providing powerful pain relief [13]. Available in transdermal patches, lozenges, nasal sprays, and injectable forms, fentanyl's versatility is matched by its potency. However, it carries a high risk of respiratory depression, sedation, and potential for overdose [14]. Methadone is used both for pain relief and as part of drug addiction detoxification and maintenance programs [15]. It binds to opioid receptors and also acts as an NMDA receptor antagonist, which may help in managing chronic pain. Methadone is available in tablet, liquid, and injectable forms. Side effects include sweating, constipation, and potential for QT prolongation, a heart rhythm disorder [16].

Tramadol is prescribed for moderate to moderately severe pain. It binds to opioid receptors and inhibits the reuptake of norepinephrine and serotonin, offering a unique mechanism among opioids [17]. Available in immediate-release and extended-release forms, tramadol is a flexible option. Side effects include nausea, dizziness, constipation, and risks such as seizures and serotonin syndrome [18]. Codeine is used for mild to moderate pain and as a cough suppressant. It is metabolized in the liver to morphine, which then binds to opioid receptors. Available in tablets and liquid formulations, often combined with acetaminophen or as part of cough syrups, codeine is commonly prescribed. Side effects include drowsiness, constipation, nausea, and potential for addiction [19].

Buprenorphine is used for pain management and opioid addiction treatment. As a partial agonist at opioid receptors, it provides pain relief with a lower risk of abuse compared to full agonists. It is available in sublingual tablets, buccal films, patches, and injectable forms. Side effects include nausea, headache, constipation, and potential for respiratory depression at high doses [20, 21].

1.3. Routes of Administration and their Clinical Significance

The routes of administration for opioids significantly influence their effects, potential for abuse, and addiction risk. Oral administration is the most common for prescribed opioids, such as oxycodone and hydrocodone. It offers ease of use, controlled dosage, and longer action duration but has a slower onset and potential for misuse through crushing and snorting or injection [22, 23]. Transdermal administration, such as fentanyl patches, provides a steady medication release with a lower abuse risk than oral forms. However, it can cause skin irritation and accidental exposure risks, particularly to children and pets [24].

Intravenous (IV) administration offers rapid action and precise dosage control but poses high addiction potential and risks of infection, overdose, and vein damage [25]. Intramuscular and subcutaneous administration are faster than oral but slower than IV, useful for controlled release yet limited by pain at the injection site and infection risk [26, 27]. Nasal and inhalation administration, involving snorting or inhaling vaporized drugs, provide rapid onset similar to IV but with high abuse potential and respiratory issues, including damage to nasal mucosa and lung complications [28, 29].

Oral administration is often preferred due to its non-invasive nature and ease of monitoring dosage [30]. However, the misuse potential through altering the form of the medication to achieve a more immediate and intense effect cannot be overlooked [31]. Transdermal systems are particularly useful in chronic pain management scenarios, providing a consistent level of pain control, which is crucial for maintaining quality of life in patients with chronic conditions [32, 33]. Despite their benefits, the challenge lies in ensuring the patches are used correctly and safely to prevent misuse or accidental exposure. IV administration, while highly effective in acute pain management and palliative care settings, presents significant risks due to the potential for rapid addiction development and the severe health consequences associated with misuse [34].

1.4. Opioid Crisis

The opioid crisis began in the late 1990s when pharmaceutical companies reassured the medical community that patients would not become addicted to opioid pain relievers. This led to an increase in prescriptions, which consequently resulted in widespread misuse of these medications. It wasn't until later that the highly addictive nature of opioids became apparent, contributing significantly to the current crisis [35].

The current state of the opioid crisis is alarming. According to the Centers for Disease Control and Prevention (CDC), over 100,000 drug overdose deaths occurred in the U.S. in 2021, with synthetic opioids like fentanyl being major contributors [36]. Although prescription rates have declined since peaking in 2012, the misuse of prescription opioids remains a significant problem [37, 38]. Furthermore, the rise of fentanyl and other synthetic opioids has exacerbated the crisis, as these substances are often mixed with other drugs, increasing the risk of overdose [39].

Several factors have contributed to the opioid crisis. Aggressive marketing by pharmaceutical companies in the 1990s and early 2000s played a crucial role. Additionally, inadequate regulation and oversight of prescription practices allowed misuse to proliferate [40]. Socioeconomic factors, such as economic decline and lack of job opportunities in certain regions, have also contributed to increased substance abuse [41]. Mental health issues, including untreated mental illnesses and trauma, often coexist with substance abuse disorders, exacerbating the problem [42, 43]. The healthcare system has also been implicated due to the lack of access to quality healthcare and addiction treatment services, as well as insufficient training for healthcare providers on pain management and addiction. Moreover, the illicit drug trade, with the increased availability of potent synthetic opioids like fentanyl, has evolved and intensified the crisis.

The societal impact of the opioid crisis is profound. Health-wise, there has been an increase in infectious diseases such as HIV and hepatitis C due to needle sharing among drug users [44]. The crisis has placed a significant strain on healthcare systems and emergency services. Socially, the crisis has had a devastating impact on families and communities, including a rise in the number of children placed in foster care. The high rates of incarceration for drug-related offenses have disproportionately affected marginalized communities. Economically, the crisis has led to a loss of productivity due to addiction and related health issues, along with high costs associated with healthcare, law enforcement, and social services [45].

1.5. Strategies to Decrease Exposure and Prevent New Addiction

Effective strategies to decrease opioid exposure and prevent addiction include education, prescription monitoring, alternative pain management, and safe prescribing practices. Education and awareness are critical; patients need to be informed about opioid risks, proper usage, and alternative pain management options, while healthcare providers require training on prescribing guidelines and non-opioid pain management [46, 47]. Prescription Drug Monitoring

Programs (PDMPs) help track prescriptions and identify misuse, while adherence to CDC guidelines ensures appropriate opioid prescribing [48, 49]. Treatment and recovery efforts have focused on expanding access to addiction treatment services, including medication-assisted treatment (MAT) with methadone, buprenorphine, and naltrexone [50]. Non-opioid pain management involves using alternatives like acetaminophen, NSAIDs, certain antidepressants, and anticonvulsants, along with non-pharmacological therapies such as physical therapy, cognitive-behavioral therapy, acupuncture, and other integrative approaches [51, 52].

Safe prescribing practices include individualized treatment plans and opioid contracts to set clear expectations and responsibilities for opioid use [53]. Healthcare providers must balance the need for effective pain management with the imperative to minimize addiction risk [54]. Risk mitigation strategies such as naloxone distribution can significantly reduce overdose fatalities. Naloxone, an opioid antagonist, can reverse the effects of an opioid overdose if administered in time, making it an essential tool in the fight against opioid overdose deaths [55, 56]. Abuse-deterrent formulations (ADFs) of opioids, designed to prevent manipulation for misuse, represent another crucial strategy. These formulations can deter common methods of abuse such as crushing for snorting or dissolving for injection, thereby reducing the potential for addiction [57, 58].

Community and policy interventions play a significant role in addressing the opioid crisis. Public health campaigns can raise awareness about the dangers of opioid misuse and the resources available for addiction treatment [59]. Legislative measures can regulate opioid prescribing and dispensing practices and support addiction treatment programs [60]. Collaboration between healthcare providers, law enforcement, policymakers, and community organizations is essential to implement these strategies effectively and ensure comprehensive support for those affected by opioid addiction [61, 62].

1.6. Regulatory Measures by the FDA to Mitigate Risks Associated with Opioid

The FDA has implemented several guidelines and regulations to mitigate the risks associated with opioid use, aiming to balance the benefits and risks of these medications:

Updated Prescribing Information: The FDA has mandated updates to the prescribing information for both immediate-release (IR) and extended-release/long-acting (ER/LA) opioid pain medications. Enhanced guidelines on prescribing practices, including boxed warnings about the risks of addiction, abuse, and misuse [63]. Improved patient counseling information to emphasize the risks associated with IR opioids and the importance of proper use [64]. These updates include enhanced warnings about the risks of misuse, abuse, addiction, and overdose. They also emphasize that IR opioids should only be used for short durations unless necessary and that ER/LA opioids are reserved for severe, persistent pain that requires long-term treatment [65-68]. Additional safety measures to ensure that healthcare providers are adequately trained in managing long-term opioid therapy [69]. Updated patient counseling materials to highlight the dangers of long-term opioid use and strategies to mitigate these risks [63]. Patients also play a crucial role in ensuring the safe use of these medications. Patients should take opioids exactly as prescribed by their healthcare provider, without altering the dose or frequency [70]. Medications should be stored securely to prevent misuse by others, particularly children and adolescents. Unused medications should be disposed of properly, using take-back programs or mail-back envelopes to prevent diversion and misuse [56]. Patients should communicate openly with their healthcare provider about their pain levels, side effects, and any concerns about their medication [43].

Risk Evaluation and Mitigation Strategies (REMS): The REMS program requires that training be made available to healthcare providers, including prescribers, nurses, and pharmacists. This training covers appropriate pain management practices, including non-opioid alternatives. The aim is to ensure that opioids are prescribed only when necessary and that providers are well-informed about the risks and safe use of these medications [71]. Also, emphasizing prescription of the lowest effective dose for the shortest duration possible and considering non-opioid alternatives first [46]. Encouraging regular monitoring of patients to adjust treatment plans and prevent misuse [70]. Starting in 2024, opioid manufacturers must provide prepaid mail-back envelopes for unused medications, enhancing disposal options and reducing the potential for misuse [64]. The 2023 blueprint includes new guidelines on safe disposal, updated statistics on opioid misuse, and revised terminology for substance use disorders [72].

Enhanced Safety Labeling: The FDA has introduced new safety labeling for all opioid medications, which includes information on the risks of opioid-induced hyperalgesia, neonatal opioid withdrawal syndrome (NOWS), and potentially harmful drug interactions. These labels also highlight the importance of educating patients and caregivers about the risks of opioids and safe disposal practices for unused medications [68, 71].

Naloxone Accessibility: The FDA has approved the over-the-counter sale of naloxone, a medication that can reverse opioid overdoses. This measure aims to make naloxone more accessible to individuals at risk of overdose, thereby reducing fatalities associated with opioid misuse [71].

Alternatives to Opioids: The FDA and healthcare providers emphasize considering non-opioid alternatives for pain management to reduce reliance on opioids. Non-opioid pain medications like acetaminophen and NSAIDs (e.g., ibuprofen, naproxen) can be effective for managing mild to moderate pain [31, 43]. Physical therapy can help manage pain through exercises and manual therapy, improving mobility and strength [73]. Cognitive Behavioral Therapy (CBT) addresses the psychological aspects of chronic pain, helping patients manage their pain more effectively through behavioral changes and coping strategies [74]. Interventional procedures such as nerve blocks, spinal cord stimulation, and other interventional procedures can provide pain relief without the risks associated with long-term opioid use [70].

1.7. Recent Advancement in Opioids

Recent advancements in opioid research aim to balance effective pain management with minimizing the associated risks. Research has focused on developing safer opioids and alternative analgesics. Key areas include biased agonism, where opioids are designed to selectively activate beneficial pathways, potentially reducing side effects like respiratory depression [7]. Researchers are also exploring non-opioid analgesics, such as cannabinoids, sodium channel blockers, and gene therapy, as alternative pain management options. Innovative approaches like vaccines that prevent opioids from crossing the blood-brain barrier and monoclonal antibodies that neutralize opioids in the bloodstream are also being investigated [75].

Non-Addictive Opioids: One of the most significant advancements is the development of non-addictive opioids. Researchers are exploring alternatives that provide pain relief without triggering the brain's reward system. For instance, oliceridine has shown promise in delivering effective pain relief with a reduced risk of dependency and fewer side effects compared to traditional opioids like morphine. Oliceridine, a biased ligand of the μ-opioid receptor, has demonstrated analgesic efficacy with a lower incidence of adverse effects in clinical trials [7, 76-78].

Biased Agonism: Biased agonism is a concept where drugs selectively activate only certain pathways of the opioid receptor, potentially reducing adverse effects. This approach aims to separate the analgesic effects from side effects such as respiratory depression and constipation. PZM21 is an example of a biased agonist that has shown efficacy in pain relief while minimizing harmful side effects. Studies have indicated that PZM21 produces long-lasting analgesia with a reduced risk of respiratory depression and addiction [75, 76, 79].

Targeted Drug Delivery Systems: Advancements in drug delivery systems have also enhanced opioid treatment. Techniques like nanoparticle-based delivery allow for targeted delivery of opioids to specific tissues or cells, potentially increasing efficacy and reducing systemic side effects and abuse potential. This targeted approach ensures that lower doses of opioids can be used, which can help mitigate the risks associated with higher doses. Nanoparticle-based systems improve the pharmacokinetics and biodistribution of opioids, leading to more efficient pain management [80].

Abuse-Deterrent Formulations (ADFs): Abuse-deterrent formulations are designed to prevent the manipulation of opioid medications for recreational use. These formulations make it difficult to crush, dissolve, or alter the drug, thereby reducing the potential for abuse. Technologies like physical barriers, chemical barriers, and aversive agents are being integrated into opioid pills to deter abuse while maintaining their therapeutic efficacy. The FDA has approved several ADFs, which have shown effectiveness in reducing abuse rates [81, 82].

Novel Analgesics: Research is also directed toward developing novel analgesics that do not interact with traditional opioid receptors. For instance, compounds targeting the nociceptin/orphanin FQ peptide receptor (NOP) have shown promise in providing pain relief without the addictive properties of conventional opioids. Drugs like cebranopadol, which target both opioid and NOP receptors, are currently under investigation for their dual pain-relief mechanisms and potentially lower addiction risks [83, 84].

Genetic and Biomarker Research: Advancements in genetic and biomarker research are paving the way for personalized pain management strategies. By understanding individual genetic variations that affect opioid metabolism and response, clinicians can tailor opioid therapies to minimize risks and enhance efficacy. This precision medicine approach aims to optimize pain management while reducing the likelihood of addiction and adverse effects. Studies have identified genetic markers that influence opioid receptor activity, which can guide the selection and dosing of opioid medications [85].

List of abbreviations:

- FDA: The Food and Drug Administration
- IV: Intravenous
- IM: Intramuscular
- IT: Intrathecal
- SC: Subcutaneous
- IR: Immediate-release
- LR: Long-acting
- ER: Extended-release
- CDC: Centers for Disease Control and Prevention
- PDMPs : Prescription Drug Monitoring Programs
- MAT: Medication-assisted Treatment
- REMS: Risk Evaluation and Mitigation Strategies
- NOWS: Neonatal Opioid Withdrawal Syndrome
- CBT: Cognitive Behavioral Therapy
- ADFs : Abuse-Deterrent Formulations
- NOP: Nociceptin/orphanin FQ Peptide

2. Conclusion

Opioids remain a cornerstone of pain management but come with significant risks that necessitate careful consideration and management. The opioid crisis has highlighted the need for better prescribing practices, comprehensive public health strategies, and continued research into safer analgesics. Ongoing advancements in understanding opioid pharmacology and developing new treatments hold promise for improving pain management while minimizing the risks associated with opioid use.

The landscape of opioid research is rapidly evolving, with significant advancements aimed at improving pain management and reducing the risks associated with opioid use. From non-addictive opioids and biased agonism to advanced drug delivery systems and abuse-deterrent formulations, these innovations hold promise for addressing the opioid crisis. Continued research and development in this field are essential for ensuring that patients receive effective and safe pain relief options.

These advancements represent a hopeful stride toward mitigating the negative impacts of opioids while preserving their essential role in pain management. The integration of these innovations into clinical practice will be crucial in shaping the future of pain treatment and combating the opioid epidemic.

Compliance with ethical standards

Disclosure of conflict of interests

The authors declare that they have no competing interests.

Authors' contributions

BS, RG, DL, PB, and PP conceptualized, researched, drafted, reviewed, and edited the article. All authors contributed equally to this paper and have read and approved the final draft.

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