*Review Article*

Journal of Pharmaceutical and Medicinal Chemistry
Volume 10 Number 1, Jan-June 2024
DOI: http://dx.doi.org/10.21088/jpmc.2395.6615.10124.1

# Comprehensive Review of Opioid Analgesics: Considerate Fundamentals

**Nikunj N. Dave[1], Naman J. Bhindora[2], Aayushi J. Mehta[3]**

**How to cite this article:**
Nikunj N. Dave, Naman J. Bhindora, Aayushi J. Mehta. Comprehensive Review of Opioid Analgesics: Considerate Fundamentals. J Pharmaceut Med Chem. 2024;10(1): 07-15.

**Abstract**

This review provides a thorough examination of opioid analgesics, covering their chemical structure, mechanism of action, classification, pharmacokinetics, and pharmacodynamics. Beginning with an exploration of the chemical structure of morphine and its analogues, the review elucidates the structural features critical for opioid activity, highlighting the diverse chemical scaffolds that underpin this class of medications. Subsequently, the review delves into the intricate mechanisms of action through which opioids exert their analgesic effects, focusing on their interactions with the mu, delta, and kappa opioid receptors within the central and peripheral nervous systems. Furthermore, the review provides a comprehensive classification of opioid analgesics based on their chemical structure, receptor selectivity, and clinical properties, delineating between natural, semi-synthetic, and synthetic opioids, as well as agonists, partial agonists, and antagonists. In addition, the review examines the pharmacokinetic properties of opioid analgesics, encompassing absorption, distribution, metabolism, and elimination pathways, and explores how individual pharmacokinetic profiles influence clinical dosing and therapeutic outcomes. Moreover, the review delves into the dynamic pharmacodynamics of opioids, elucidating dose response relationships, onset and duration of action, and factors influencing inter-individual variability in response to opioid therapy. Finally, the review underscores the clinical implications of opioid pharmacology, emphasizing the importance of judicious prescribing practices, individualized treatment approaches, and multidisciplinary collaboration in optimizing pain management while mitigating the risks of opioid related adverse effects, tolerance, dependence, and misuse.

**Keywords:** Opioid Analgesic; Morphine; Opioid receptor

**Author's Affiliations:** [1]Assistant Professor, Department of Pharmaceutical Chemistry, [2,3]Research Scholar, C.U. Shah College of Pharmacy & Research, Wadhwan 363030, Gujarat, India.

**Corresponding Author: Nikunj N. Dave,** Assistant Professor, Department of Chemistry, C. U. Shah College of Pharmacy & Research, Wadhwan 363030, Gujarat, India.

**Email:** nikunjndave@gmail.com

**Received on:** 01.06.2023

**Accepted on:** 30.08.2023



## INTRODUCTION

Analgesics refer to drugs used to alleviate pain, while opioids constitute a widely employed group of medications for relieving moderate to severe pain. They are alternatively known as opiates, opioid analgesics, or narcotics and can originate naturally or synthetically from opium derived sources. Opiates pertain specifically to substances

containing opium or those structurally akin to morphine, such as heroin, codeine, and morphine itself, whereas opioids encompass a broader spectrum, including synthetic, semi-synthetic, naturally occurring, and endogenous compounds interacting with opioid receptors in the body.[1,2] The opiate structure holds historical significance as one of the earliest medicinal compounds known, with opium extraction dating back to 3,400 B.C. from the opium poppy (Papaver Somniferum) shown in fig. 1, in lower Mesopotamia. Morphine's isolation in 1805 by German pharmacist Friedrich Serturner marked a significant advancement in opioid pharmacology, its widespread use facilitated by the invention of the hypodermic syringe circa 1855.

**Fig. 1:** Opium Poppy plant

Opium yields other naturally occurring alkaloids like codeine, papaverine, and the baine. However, the scope of opium analgesics extends beyond pain relief, encompassing potential side effects and risks of addiction. In the nineteenth century, numerous writers and artists fell victim to addiction due to sustained opioid use, prompting regulatory measures in the twentieth century to restrict their medical and scientific utilization. Prolonged narcotic drug consumption may induce tolerance, necessitating escalating doses to maintain therapeutic efficacy, leading to physical dependence and withdrawal symptoms upon cessation, culminating in addiction.[3] The distinctions between opioid tolerance, dependency, and addiction are delineated in the table provided.

**Table 1:** Opioid Tolerance, Dependency and Addiction

| Opioid Tolerance | Opioid Dependency | Opioid Addiction |
|---|---|---|
| Repeated use of opioids leads to decreased response, due to which an increased dose is required to produce the same effect | Normal functioning of the body is adjusted as per opioid intake. Decreased use of medication to overcome dependency would lead to the occurrence of 'withdrawal/unusual symptoms' | OUD (Opioid Use Disorder) occurs mainly after the person is tolerant and dependent on opioids and when all methods to overcome the dependency are unsuccessful |

## *Brief overview of the opioid epidemic and its impact on public health*

The opioid crisis, characterized by a significant surge in abuse and fatal overdoses, has been labeled a uniquely American dilemma. Overdosing on high opioid doses can lead to respiratory depression, respiratory failure, and ultimately, death. The fatality toll from drug overdoses soared over sixfold from 1999 to 2023, with a distressing 18% spike between 2020 and 2021 alone. Opioid usage surged by 20% during the same period, while synthetic opioid linked deaths rose by 25%. Tragically, nearly 645,000 individuals lost their lives to opioid abuse and overdoses from 1999 to 2021.[4]

The crisis unfolded in three distinct waves: the first, triggered by heightened opioid prescriptions in the 1990s; the second, commencing in 2010, saw a surge in heroin related deaths, and the third, starting in 2013,[5] witnessed a rise in fatalities involving synthetic opioids. Despite India's relatively lower opioid prevalence compared to the USA, there exists significant regional variation in opioid usage, with Uttar Pradesh emerging as a hotspot. However, Mizoram and Nagaland suffer the most severe repercussions of the epidemic in India. Data from the National Institute of Drug Abuse illustrates, in Fig. 2, the catastrophic escalation of opioid related fatalities in the US from 1999 to 2021, while Fig. 3 from GS Score highlights the alarming trends of drug abuse in India.[6]

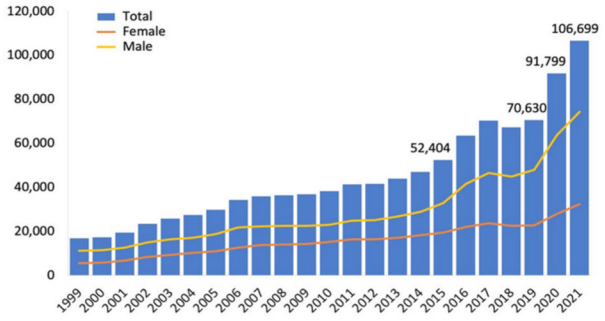


**Fig. 2:** Number of deaths due to drug overdose

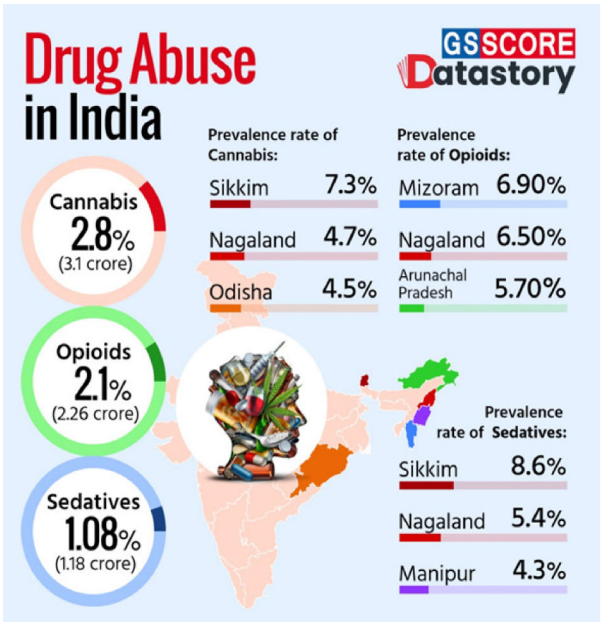


**Fig. 3:** Drug Abuse in India ***(Source:*** *https://iasscore.in/centers/gs-score-delhi)*

## *Classification and Mechanism of Action*

Opioids can be classified based on occurrence as (i) Natural compounds, (ii) Semi-Synthetic compounds and (iii) Synthetic derivatives; examples of (i) Naturally occurring opioids are Morphine, Codeine, Thebaine, Papaverine; (ii) Semi-synthetic opioids are Diacetylmorphine (Heroin), Pholcodine, Ethyl morphine, Oxycodone, Hydrocodone, Hydromorphone, Oxymorphone, Dihydromorphone, Buprenorphine; (iii) Synthetic Opioids are divided into 4 groups as, (a) Morphine Derivatives, e.g. Butorphanol, Levorphanol (b) Phenylpiperidine derivatives, e.g. Pethidine, Alfentanil, Fentanyl, Sufentanil, Remifentanil (c) Benzomorphan Derivatives, e.g. Pentazocine, Phenazocine (d) Diphenylheptane Derivatives, e.g. Methadone, Propoxyphene. For a better understanding, the classification is given in Fig. 4.

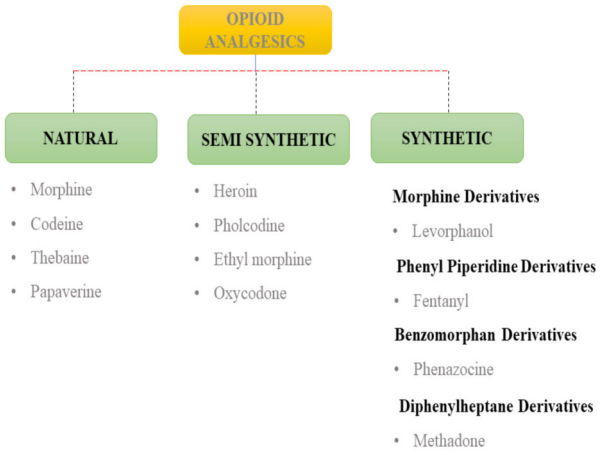


**Fig. 4:** Classification of Opioid Analgesic

Classification of opioids can also be done based on the type of receptor (site) at which its effect is exerted, namely: delta {δ}, kappa, and mu{μ} (named after vas deferens, ketocyclazocine, and morphine respectively). Later on, these names were changed to DOR, KOR, and MOR respectively; in 1996, these receptors were renamed to OP1, OP2, and OP3 respectively by IUPHAR (International Union of Pharmacology), and in 2000, IUPHAR renamed the nomenclature and changed it to DOP, KOP, and MOP respectively. All these receptors are G-protein coupled receptors (GPCRs). Endogenous ligands active at these receptors were derived from the parent compounds which were obtained from 3 pro-hormone precursors. Table 2 shows opioid receptors. The fourth receptor, which was also a G-protein coupled receptor, was identified in 1994, namely, Nociceptive receptor (NOP). Polypeptide precursor pre-pro-nociceptin was the precursor compound from which its endogenous ligand, nociceptin/orphanin FQ (N/OFQ) was derived.

**Table 2:** Opioid receptors, IUPHAR 2000 Nomenclature, ligands and their pro-hormone

| Receptors' Type | Iuphar 2000 Nomenclature | Pro-hormone | Endogenous ligand (peptide) |
|---|---|---|---|
| Delta (δ) | DOP | Pro-enkephalin | [Leu]-enkephalin<br>[Met]-enkephalin |
| Kappa (κ) | KOP | Pro-dynorphin | Dynorphin-A<br>Dynorphin-B |
| Mu (μ) | MOP | Pro-opiomelancortin (POMC) | Beta (β)- Endorphin<br>Endorphin-1<br>Endorphin-2 |
| Nociceptive | NOP | Pre-pro-nociceptin | N/OFQ |

## *Mechanism of Action*

All the opioid receptors, delta, kappa, and mu are GPCRs and are situated on the presynaptic (prejunctional) nerve and they show an inhibitory effect by reducing the release of neurotransmitter (i.e., noradrenaline, dopamine, 5-HT {5-Hydroxy tryptamine)} and glutamate. Activation of opioid receptors decreases intracellular cAMP formation and opens $K^+$ channels or suppresses voltage-gated N-type $Ca^{2+}$ channels. These cause hyper-polarization in synaptic junctions and a decrease in neurotransmitter release. Out of all opioid receptors, delta (δ) receptors mediate spinal analgesia, affective behavior, reinforcing actions, respiratory depression, and reduced GI motility whereas kappa receptors cause miosis, sedation, dysphoria, respiratory depression, hallucination, and nicotinic effects. Through K1 receptor subtypes, they tend to mediate spinal analgesia, and through K3 subtype - supra-spinal analgesia. Mu (μ) receptors including $\mu_1$ and $\mu_2$ in which $\mu_1$ mediate supra-spinal analgesia, the $u_2$ receptor mediates spinal analgesia and its subtypes mediate gastric motility reduction and respiratory depression. These actions aren't shown if the receptors are blocked by antagonists like naloxone, naltrexone, etc.[7,8]

## *Chemical Structure and SAR*

Morphine is the first isolated opium alkaloid. Its molecular formula is $C_{17}H_{18}NO_3$. Its IUPAC name is 17-methyl-7,8-didehydro-4,5α-epoxymorphinan-3,6α-diol and IUPAC Id is (4R,4aR,7S,7aR,12bS)-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol. The structure of Morphine shown in Figure 5, consists of five rings in which ring 'A' is a phenyl ring which is essential for analgesic activity, ring 'B' is cyclohexyl, ring 'C' has one pi bond at 7,8 position, ring 'D' is a five-member nitrogen containing ring, 'E' is tetrahydrofuran moiety. The structure possesses one phenolic hydroxyl group, ether bridge, allylic alcohol, and tertiary nitrogen.

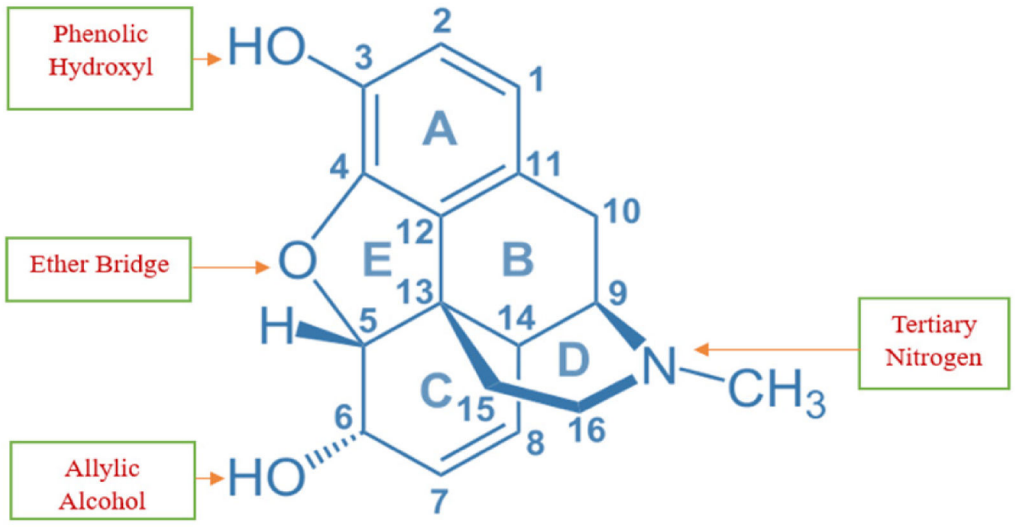


**Fig. 5:** Chemical Structure of Morphine

Replacing the hydroxyl group at carbon 3 and 6 generates different analogs of morphine displayed in Table 3. The phenolic hydroxyl group at carbon 3 is essential for optimum analgesic effects and alteration of the hydroxyl group with acetyl, methoxy or ethoxy decreases the analgesic activity and increases toxicity. On the other side alteration except carbonyl group on alcoholic hydroxyl group at carbon 6 increases the analgesic effect of morphine. The Methyl group attached to tertiary nitrogen is necessary for morphine to act as an agonist however allyl or propyl groups make it an antagonist. Removal of double bonds at carbon 7,8 improves potency. Removal of oxygen in ring 'E' leads to the preparation of compounds known as 'Morphinans' which also have useful analgesic effects.[9,10]

**Table 3:** Analogs of Morphine

| Position in Morphine structure | Substitution | Name after substitution |
|---|---|---|
| 3 | $-OCH_3$ | Codeine |
| 3, 6 | $-OCH_3$, $-OCH_3$ | Thebaine |
| 3, 6 | $-OCOCH_3$, $-OCOCH_3$ | Heroine |
| 3, 6 | $-OCH_3$, -C=O | Hydrocodone |
| 3,6 | $-OCH_3$, -C=O | Oxycodone |
| 6 | -C=O | Oxymorphone |
| 7-8 | Double bond absent | Dihydromorphine |
| 3, 7-8 | $-OCH_3$, Double bond absent | Dihydrocodeine |
| 6, 7-8, 3° N | -C=O, Double bond absent, $-CH_2-CH=CH_2$ | Naloxone |

## *Pharmacokinetics and Pharmacodynamics*

Pharmacokinetic properties of opioids include route of administration, rate of administration, physicochemical properties of the drug, and rate of onset of drug action. It includes absorption, distribution, metabolism, and excretion (ADME) parameters of drugs. The route of drug administration strongly affects the rate of onset of drug action due to differences in absorption by different membranes and its exposure to first pass metabolism. The oral absorption of morphine is unreliable because of high and variable first pass metabolism, in contrast, intravenously administered morphine has a faster absorption rate; oral bioavailability is $1/6^{th}$ to $1/4^{th}$ of parenterally absorbed drug, and about 30% is bound to plasma proteins.[11] Faster absorption leads to faster and greater therapeutic effects. After the drug reaches the systemic circulation, it is distributed to other cells and tissues with the help of a concentration gradient (tissues lack the drug which causes the drug to travel from high concentration, i.e., systemic circulation to low concentration, i.e., the tissues), which continues till equilibrium is attained. For instance, Morphine's distribution is more in the spleen, liver, and kidney than in plasma. It can affect the fetus from the mother as it easily crosses the placental barrier.[12]

Once distributed, the drug undergoes metabolism (biotransformation) conversion of lipophilic (non-polar) drug to hydrophilic (polar) drug by chemical alteration so that the drug can be easily excreted from the body without any renal reabsorption. A morphine-6-glucuronide metabolite is formed from morphine in the liver by glucuronide conjugation which contributes to analgesia. The parenteral dose effect lasts 4-6 hours and the average half-life of morphine is 2-3 hours. Excretion (elimination) of absorbed drugs and their metabolites occurs via urine, sweat, saliva, milk, feces, etc. In the case of morphine, it is completely excreted from the body within 24 hours, however, small amounts may persist due to enterohepatic circulation.[13]

Opioids produce analgesic effects by binding to their receptors. All its receptors are G-protein coupled receptors (GPCRs) coupled with the decrease in cyclic adenosine monophosphate (cAMP) as well as they are also associated with the increased opening of potassium channels ($K^+$) which produces the hyper polarisation and closing of the calcium channels which results in the prevention of the depolarization; in this way, the opioid receptors mainly produce the inhibitory response. Opioids produce a central inhibition (mainly related to opioid receptors) which produces sedation as well as nociception, that's why they are used as analgesic agents; but opioids can also produce few of the stimulatory actions on few of the organs which may not be related to their action on opioid receptors. 2 types of responses are produced by opioids, namely, inhibitory and

stimulatory response. Inhibitory responses are shown on nociceptive receptors, GI smooth muscle, respiratory system, ureter, bladder, and uterus. On nociceptive neurons, they produce analgesia by decreasing nociception (decreasing pain sensation) by inhibition. On prolonged use, they produce tolerance and can cause hyperalgesia (increased pain sensation) and allodynia (pain caused even by non-painful stimuli).[14] They also decrease heart rate by acting on the medulla (bradycardia). On μ receptors drugs like morphine, heroin, fentanyl, etc. produce euphoria, and on κ receptors drugs like pentazocine produce dysphoria. On GI smooth muscle they decrease GI motility which causes constipation which helps treat diarrhoea and also decreases gastric emptying rate which reduces the absorption of other drugs co-administered with opioids. On the respiratory system, they inhibit the activity of the respiratory centre which leads to reduced sensitivity to $PCO_2$ (Partial Pressure of $CO_2$) which results in the accumulation of $CO_2$ which causes respiratory depression (this effect is more associated with μ receptors).[15] On other smooth muscles, opioids produce relaxation of other smooth muscles like the uterus, and bladder (at a therapeutic level, these are very less significant). Stimulatory responses are shown on mast cells, oculomotor nerve, gall bladder, and CTZ (chemoreceptor trigger zone). On mast cells, opioids stimulate mast cells, so that they can be degranulated and release one of the important mediators such as histamine which causes symptoms like itching, and skin rashes and produces vasodilatation resulting in hypotension (in this way, opioids produce an allergic response as well as decrease blood pressure by releasing histamine).[16] On the oculomotor nerve, they stimulate the oculomotor nerve which acts on the eye to produce pupillary constriction and cause miosis. They decrease the pupillary size and produce one of the conditions called 'pinpoint pupils' which is used to identify the opioids. They increase the contraction of the gall bladder as well as of the biliary sphincter and because of this they increase the intra-biliary pressure; in this way, opioids can increase the biliary colic by increasing the biliary pressure, that's why, they are contraindicated in controlling the pain associated with the gall stones. Opioids act on one of the regions in CTZ, i.e., the 'Area Postrema' and stimulate this center and produce nausea and vomiting. Particularly, morphine stimulates the CTZ to induce nausea and vomiting, and its derivative apomorphine is used as an emetic in case of any poisoning to induce nausea and vomiting.[17]

## *Clinical Applications and Guidelines*

Multiple opioids are available for clinical application, such as morphine, hydromorphone, levorphanol, oxycodone, and fentanyl. The evolution of opioid analgesics is depicted in Fig. 6. Historically, opioid analgesics have been widely utilized for various types of pain management. They are appropriately administered for short-term relief, particularly post-surgery or in response to medical conditions. Acute pain management is crucial for facilitating recovery from surgery or trauma, and opioid analgesics have proven efficacy in this regard. Additionally, they are often employed as part of a multimodal analgesic approach in conjunction with paracetamol, non-steroidal anti-inflammatory drugs, and local anesthetics. Systemic administration of opioids via parenteral routes (intravenous, intramuscular, or subcutaneous) typically results in faster onset compared to oral administration. A single dose of opioid analgesics for acute pain aims to achieve 50% maximum pain relief within four to six hours, as indicated by the Number Needed to Treat (NNT). Higher NNT values correspond to less effective treatment. Treatments with NNTs ranging from 2 to 5 are generally deemed effective for managing acute pain.[18]

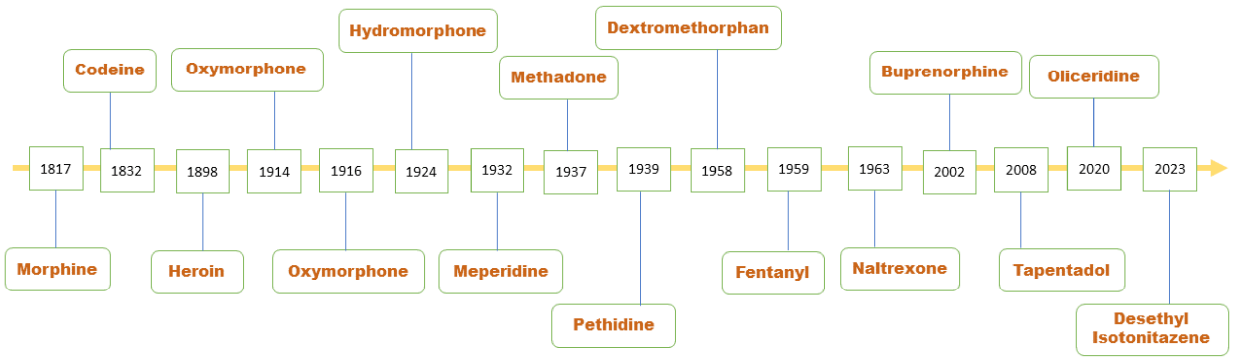


**Fig. 6**: Timeline showing the development of different opioid analgesic

### *Adverse Effects and Risk Mitigation*

The increased usage of opioids correlates with elevated risks of overdose, side effects, and fatalities. Common side effects encompass tolerance, constipation, nausea, vomiting, dizziness, pruritus, dry mouth, withdrawal symptoms, sedation, respiratory depression, and addiction.[19]

Adenylyl cyclase is responsible for synthesizing cyclic adenosine monophosphate (cAMP). Elevated cAMP levels activate neurons, while decreased levels inhibit them. The G alpha subunit of the mu (μ) opioid receptor inhibits adenylyl cyclase, thus reducing cAMP synthesis. Prolonged opioid use diminishes the ability to decrease cAMP, resulting in tolerance.[20] In response, the body seeks homeostasis, leading to an anticipatory increase in adenylyl cyclase activity, overshooting cAMP levels above normal. Consequently, higher opioid doses are required to lower cAMP levels and inhibit neurons, leading to tolerance development. Withdrawal symptoms occur when opioid use is reduced, as compensatory cAMP levels are no longer counteracted, causing certain neurons to become overactive, ultimately resulting in addiction.

Opioid use diminishes gastrointestinal motility, leading to constipation. Opioid overdose desensitizes respiratory neurons to $PCO_2$, causing $CO_2$ accumulation, which suppresses the brain's respiratory drive, potentially resulting in death.

Managing opioid related side effects is crucial. Tolerance typically develops within the initial days of treatment, with pruritus and constipation persisting throughout. Prescribing small quantities of anti-emetics initially can be beneficial. Central side effects like dizziness and drowsiness may improve over time, but patients should be counseled regarding potential impairments in driving and other tasks requiring coordination and concentration.[21]

Peripherally restricted opioid antagonists, such as oral naloxegol, have shown modest benefits in improving constipation. Lifestyle adjustments, including increased fluid, fruit, and fiber intake, alongside stool softeners and stimulant laxatives, are often necessary to alleviate constipation. Patients should be counseled on opioid associated side effects and their management prior to prescription.

Opioid overdose can be reversed by antagonists like naloxone, which binds to opioid receptors, displacing opioids like morphine. Although structurally similar to morphine, naloxone cannot activate these receptors, making it an effective antagonist. Naloxone kits, available in certain drug stores, play a crucial role in combating opioid overdose.[22]

### *Opioid Crisis and Public Health Implications*

As per the United Nations report 13% of drug misuse where there in India below 20 age. From past year opioid misuse rates were 2.13% to 4.26% at 13 years of age, 3.84% to 7.60% at 15 years of age, 4.00% to 10.88% at 17 years of age, and 4.96% to 12.25% at 19 years of age.[23] This establishes that the differences grow as adolescents become older. Opioid use has negative effects on personal relationships and finances. Opioids such as heroin are illegal drugs of abuse.

Symptoms of addiction include uncontrollable cravings. It is a long-lasting (chronic) disease that causes major health, social life, and economic problems. They are a class of drugs that act on the nervous system and produce feelings of pleasure and pain relief.[24] ome opioids are prescribed for healthcare which help to manage acute and chronic pain. Commonly prescribed opioids are oxycodone, fentanyl, buprenorphine, methadone, oxymorphone, hydrocodone, codeine, and morphine. Opioids have a high potential of causing addiction in some people, even when they are no longer required or prescribed.

Overdose deaths In 2023 112,000 people where died due to drug overdose in 2023 it was on the top in just 12 months. In India, there was a 70% rise in drug consumption in the last nine years. Over 85% of drug overdose deaths in 2023. To save lives from drug overdose the Centres for Disease Control and Prevention (CDC) wanted to educate young adults (ages 18-34) who misuse drugs. That can save the lives of people who use drugs and highlight actions the public can take to help prevent overdose.[25]

### *Future Directions and Research*

Due to the numerous side effects associated with opioids, there has been a necessity to explore analgesics devoid of addictive properties or with reduced addictive effects. These analgesics aim to provide safer and more effective pain relief with fewer adverse effects. The development of advanced analgesics can be categorized into five main approaches. Firstly, efforts have been made to enhance the safety and efficacy of existing drugs by developing novel dosage forms or formulations. This includes the creation of extended release or abuse resistant formulations of drugs like morphine, oxycodone, and tramadol, as well as alternative delivery methods such as patches for

agents like fentanyl, lidocaine, and diclofenac for localized administration.

Secondly, researchers have developed compounds targeting known mechanisms, particularly opiates and NSAIDs. Thirdly, combination products have been formulated by combining existing compounds to mitigate side effects and enhance efficacy. Examples include naproxen combined with the proton pump inhibitor esomeprazole (Vimovo) and oxycodone combined with ibuprofen.

Fourthly, some analgesic medications originally used for other therapeutic indications have been repurposed for pain treatment, while novel analgesics have been designed from known mechanistic classes of compounds. Examples include rofecoxib, tapentadol, pregabalin, celecoxib, duloxetine, and ropivacaine.

Lastly, therapeutics have been developed based on the identification of novel mechanisms. Examples include Sativex, which operates via a cannabinoid based mechanism, and Prialt (ziconotide; Endo), an N-type calcium channel blocker.

Therefore, there remains a pressing need for the development of novel analgesics to meet the diverse requirements of patients and improve pain management practices.

## CONCLUSION

The comprehensive review of opioid analgesics presented herein underscores the multifaceted nature of these medications in pain management. From their intricate chemical structures to their diverse mechanisms of action and pharmacokinetic profiles, opioids occupy a central role in addressing acute and chronic pain across various clinical contexts. However, the wide spread use of opioids is accompanied by significant challenges, including the risk of tolerance, physical dependence, addiction, and adverse effects. The review highlights the importance of a balanced approach to opioid therapy, integrating evidence based guidelines, judicious prescribing practices, and vigilant monitoring to optimize therapeutic outcomes while minimizing the potential for harm. Furthermore, the review emphasizes the need for continued research and innovation in opioid pharmacology, including the development of novel analgesic agents with improved safety and efficacy profiles, as well as the exploration of opioid sparing strategies and alternative modalities for pain management. Ultimately, the effective and responsible use of opioid analgesics necessitates a holistic approach that prioritizes patient safety, individualized treatment plans, and interdisciplinary collaboration among healthcare providers. By navigating the complexities of opioid therapy with diligence and foresight, clinicians can uphold the principles of beneficence and nonmaleficence while striving to alleviate suffering and improve the quality of life for patients experiencing pain.

### *Conflict of Interest*

Authors declare no conflict of interest

## REFERENCES

1. Graham L Patrick. The opioid analgesics. In: An Introduction to Medicinal Chemistry. Oxford: Oxford University Press; 2013. p. 632-658.
2. Hasan Pathan, John Williams. Basic opioid pharmacology: an update. British Journal of Pain 2012;6(1):11-16.
3. Health Promotion. PCD provides an open exchange of information and knowledge among researchers.
4. Shipton EA, Shipton EE, Shipton AJ. A Review of the Opioid Epidemic: What Do We Do About It?". Pain and Therapy 2008;7(1):23–36.
5. World Health Organization. Opioid overdose. August 4, 2021. Archived from the original on December 1, 2014.
6. Ambekar A, Agrawal A, Rao R, et al. Magnitude of Substance Use in India. New Delhi: Ministry of Social Justice and Empowerment, Government of India 2019.
7. V. Alagarswamy. Narcotic Analgesics. In: Textbook of Medicinal Chemistry: Elsevier; 2010. p. 247-285.
8. Stein, Christoph MD, Priv Doz. Peripheral Mechanisms of Opioid Analgesia. Anesthesia & Analgesia 1993. 76(1);182-191.
9. Spetea, M.; Schmidhammer, H. Recent Chemical and Pharmacological Developments on 14-Oxygenated-N-methylmorphinan-6-ones. Molecules 2021, 26, 5677.
10. Rita T, Agostino M, Carmela P, Lorella P. Benzomorphan scaffold for opioid analgesics and pharmacological tools development: A comprehensive review. European Journal of Medicinal Chemistry, Volume 148, 2018. 410-422.
11. KD Tripathi. Opioid Analgesics and Antagonists. In: Essentials of Medical Pharmacology. Jaypee Brothers Medical Publishers (P) Ltd.; 2013.469-485.
12. Rajiv Balyan, David Hahn, Henry Huang, Vidya Chidambaran. Pharmacokinetic and pharmacodynamic considerations in developing a response to the opioid epidemic. Expert Opin Drug Metab Toxicol. 2020 Feb;16(2):125-141.

13. Andrea M Trescot MD, Sukdeb Datta MD, Marion Lee MD, Hans Hansen MD. Opioid Pharmacology. Pain Physician 2008;11:S133-S153.
14. R.T. Jones. Euphoria vs. cocaine plasma concentrations after nasal administration (20% solution). In. C.N. Chiang, R.L. Hawks (eds.), NIDA Research Monograph 99 (Research Findings on Smoking of Abused Substances); 1990. p. 30–41.
15. McCleane G, Smith H. Opioids for persistent noncancer pain. Med Clin N Am 2007;(91):177-197.
16. Corbett AD, Henderson G, McKnight AT, Paterson SJ. 75 years of opioid research: the exciting but vain quest for the Holy Grail. British J Pharmacology 2006;147:S153-S162.
17. Pan Z, Hirakawa N, Fields HL. A cellular mechanism for the bidirectional pain-modulating actions of orphanin FQ/nociceptin. Neuron May 26; 515–522.
18. Dolin SJ, Cashman JN & Bland JM. Effectiveness of acute postoperative pain management: I. Evidence from published data. British Journal of Anaesthesia 2002; 89:409-23.
19. John M Swegle, Craig Logemann. Management of Common Opioid Induced Adverse Effects. Am Fam Physician 2006;74(8):1347-1354.
20. Mahmoud Reza Khansari, Masour Reza Sohrabi, Farhad Zamani. The Usage of Opioids and their Adverse Effects in Gastrointestinal Practice: A Review. Middle East J Dig Dis 2013 Jan;5(1):5-16.
21. Side effects of opioids. Faculty of Pain Medicine of the Royal College of Anaesthetists. https://fpm.ac.uk/opioids-aware-clinical-use-opioids/side-effects-opioids#:~:text=Most%20commom%20side%20effects%20are,extremely%20common%20with%20opioid%20therapy.
22. World Health Organization. Opioid Overdose. 29 August 2023.
23. Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health (NSDUH): methodological summary and definitions. Accessed October 7, 2022.
24. National Institute on Drug Abuse. The science of drug use and addiction: the basics.
25. Mattson CL, Tanz LJ, Quinn K, Kariisa M, Patel P, Davis NL. Trends and Geographic Patterns in Drug and Synthetic Opioid Overdose Deaths — United States, 2013-2019.2021;70:202–207.