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THE USE OF PAINKILLERS IN MEDICAL PRACTICE, SIDE EFFECTS AND THE RELEVANCE OF THE SEARCH FOR HIGHLY EFFECTIVE AND SAFE DRUGS

Pakhlavon Qakhramonovich Turdiev
Head teacher of the Department of Pharmacology of
Tashkent State Medical University, Tashkent, Uzbekistan.

Madina Khursand qizi Khajibaeva
Student of the group 303B, 3nd Faculty of General Medicine of
Tashkent State Medical University, Tashkent, Uzbekistan.

Madinabonu Ilkhomjon qizi Mo‘ydinova
Student of the group 303B, 3nd Faculty of General Medicine of
Tashkent State Medical University, Tashkent, Uzbekistan.

Musaffo Alijon qizi To‘rajonova
Student of the group 305B, 3nd Faculty of General Medicine of
Tashkent State Medical University, Tashkent, Uzbekistan.

Marjona Sherali qizi Khamraeva
Student of the group 307B, 3nd Faculty of General Medicine of
Tashkent State Medical University, Tashkent, Uzbekistan.

Otabek Alijon o‘g‘li Nazarov
Student of the group 105A, 2nd Faculty of Dentistry of
Tashkent State Medical University, Tashkent, Uzbekistan.
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Abstract. In order to reduce discomfort and enhance the quality of life for those with acute or chronic pain, pain management is an essential component of healthcare. The main strategy for managing pain is pharmacological approaches, which include a wide range of medications that function via various mechanisms. According to the review's findings, a multimodal strategy that combines several analgesics can improve pain management while reducing side effects. In order to maximize the results of pain management, it highlights the significance of evaluating the severity of pain, identifying the underlying cause, and applying evidence-based recommendations. In order to minimize side effects and achieve the best possible pain relief, pharmacological pain management techniques are a crucial part of pain management strategies. A review of new developments and potential paths in pharmacological pain management, such as innovative drug targets and improvements in drug delivery systems, is included in the article's conclusion. In order to treat moderate to severe acute and chronic pain, opioids are frequently employed as therapeutic agents. However, because they cause analgesic tolerance, addiction, and a variety of behavioral side effects that frequently lead to patient non-compliance, these kinds of analgesic medications have several potential drawbacks. Since opium and opioids have historically been used to treat pain, the precise processes underlying their negative side effects after chronic usage are complex and poorly understood. Due to aging-related physiological changes and decreased metabolic capacity, older persons experience greater chronic pain from cancer and non-cancer conditions than younger adults. As a result, they experience more adverse reactions to opioid medications.

Keywords. morphine, opioids, analgesia, behavior, side effects, chronic pain, tolerance.

Introduction. The International Association for the Study of Pain (IASP) defines pain as an unpleasant emotional and sensory experience that is either articulated in terms of or connected to actual potential tissue damage. Nociceptive, neuropathic, and nociplastic pain (a combination of both that cannot be fully characterized as nociceptive or neuropathic) are the three types of pain. The brain receives nociceptive pain as a warning signal about potential non-neural tissue injury. On the other hand, neuropathic pain typically arises from a disease, toxin, or infection that damages neural tissue. The third kind of pain, known as nociplastic pain, is a complicated pain that is not fully understood but is most likely brought on by a change in the way neurons react to pain and an elevated level of central nervous system (CNS) sensitivity. Patients with cancer and other long-term chronic illnesses frequently experience nociceplastic pain, which typically lasts longer than three months and manifests as symptoms including hyperalgesia and localized pain [1-5]. Physical, psychological, and social variables all play a part in the subjective experience of pain. Numerous factors, such as illness, injury, inflammation, and nerve damage, can cause it. An individual's ability to carry out everyday tasks, execute employment commitments, and engage in social relationships can all be significantly impacted by pain. The complicated process of pain perception includes the activation of sensory neurons, the passage of chemical and electrical signals via cerebral pathways, and the interpretation of these signals by higher brain regions. Numerous systems are involved in the production and regulation of pain perception. The activation of nociceptors—specialized sensory neurons that react to unpleasant stimuli—is one way. Ion channels that are triggered by heat, acid, and other unpleasant stimuli, such as acid-sensing ion channels (ASICs) and transient receptor potential vanilloid 1 (TRPV1), are expressed by nociceptors [6-11]. When a neuron is depolarized by these ion channels, excitatory neurotransmitters like glutamate and substance P are released. These neurotransmitters activate nearby neurons and set off a series of chemical and electrical signals that ascend to the spinal cord. These signals can also be transmitted via brain circuits like the spinothalamic tract. These signals are sent to secondary neurons in the spinal cord, which are in charge of sending the data to higher brain regions. All things considered, the mechanisms underlying pain perception are intricate and entail the activation and modification of numerous brain pathways and signaling molecules. It is essential to comprehend these systems in order to design efficient pain treatment. It is impossible to overstate the frequency and importance of pain as a medical concern. It impacts a sizable section of the populace and has profound effects on people, healthcare institutions, and society as a whole. Effective pain management and better patient outcomes continue to be top priorities in the medical field. A multidisciplinary strategy that incorporates both pharmaceutical and non-pharmacological techniques is necessary for effective pain management, which is a crucial component of healthcare [12-19]. Pain, emotions, immunity, and other physiological reactions are all regulated by the opioid system, a physiological control system. Numerous endogenous opioid peptides and several opioid receptor types in the central nervous system and peripheral nervous system are involved in the coordination and communication of the opioid system. Numerous sensory, emotional, motivational, and cognitive processes as well as addictive behaviors are also strongly modulated by this system. It also has a role in various physiological processes, such as immunological, endocrine, respiratory, gastrointestinal, and stress reactions. Opioid ligands, which attach to particular opioid receptors to produce analgesia and behavioral consequences in vivo, control these reactions. Therefore, it is crucial to first grasp the distinct functions of each type of opioid receptor in order to comprehend the pharmacological effects of particular opioids [20-27].

The main purpose of the presented manuscript is to provide a brief overview of the use of painkillers in medical practice, side effects, and the relevance of the search for high-potency painkillers based on the results of reputable scientific research.

Receptors for Opioids. In 1954, the existence of opioid receptors was initially suggested. The International Union of Basic and Clinical Pharmacology (IUPHAR) and the British Pharmacological Society (BPS) joint IUPHAR/BPS Guide to Pharmacology, however, states that opioid receptors are divided into μ (Mu: MOP), δ (delta: DOP), and κ (kappa: KOP) receptors in addition to the non-classical nociception (NOP) receptor. However, the first evidence of the multiplicity of opioid receptors was first reported in 1976. The amino acid makeup of opioid receptors is roughly 60% similar to that of seven-

transmembrane helical G protein-coupled receptors (GPCRs). These receptors are linked to heterotrimeric Gi/Go proteins and have an extracellular N-terminus and an intracellular C-terminus. By creating ligand-receptor interactions in the binding pockets of the receptor, which are located in the transmembrane helices, opioid ligands bind to opioid receptors [13-19]. The binding pocket of opioid receptors can be separated into two distinct regions: the extracellular side, which contains divergent residues that confer selectivity to different types of opioid receptors (the "address" region), and the intracellular side, which is highly conserved for opioids (the non-specific "message" region). The type of opioid ligand also affects binding. All four opioid receptors' initial molecular structures were published in multiple studies in 2012. In the investigation on the role of specific opioid receptors and their ligands in pain modulation, antinociceptive tolerance and adverse behavioural effects, the generation of knockout animals has provided significant knowledge on the in vivo physiological role of the opioid system. For example, in MOP receptor knockout mice, MOP receptor agonist-induced antinociception and their associated side effects (e.g., hyperlocomotion, respiratory depression, inhibition of gastrointestinal tract transit, reward and withdrawal effects) were effectively abolished [23-28].

Adjuvant analgesics, corticosteroids, and both opioid and non-opioid analgesics are pharmacological approaches to pain management. For the treatment of mild to moderate pain, non-opioid analgesics are frequently employed. Strong painkillers called opioid analgesics are used to treat moderate to severe pain. However, they are linked to a number of negative side effects, such as constipation, respiratory depression, and drowsiness. Additionally, there is a significant danger of addiction and dependence with opioid medicines. Antidepressants and anticonvulsants are examples of adjuvant analgesics that are used to improve pain relief. Strong anti-inflammatory drugs called corticosteroids are used to treat inflammation-related pain. They are frequently used to treat pain brought on by ailments including back discomfort and rheumatoid arthritis. Twenty By altering the nervous system's activity through methods like spinal cord stimulation, deep brain stimulation, and transcutaneous electrical nerve stimulation, emerging treatments like neuromodulation for pain provide creative ways to reduce chronic pain. When choosing the best drug and dose schedule for pain management, patient-specific criteria are crucial [4-11]. The type and severity of the patient's pain is one crucial set of parameters to take into account. The patient's choice of medication is influenced by the type and intensity of their pain. The existence of underlying medical issues is another important aspect. In order to reduce possible side effects or drug interactions, patients with comorbidities, such as liver or kidney illness, cardiovascular disorders, or gastrointestinal problems, may need to have their prescription choices or dosages adjusted. Age-related physiological changes can also impact medication selection. Elderly patients may experience altered pharmacokinetics and pharmacodynamics, making them more susceptible to adverse effects. As a result, they may require lower doses or alternative medications that are better tolerated. Evaluation of the patient’s medication profile is essential to identify potential drug interactions. Some medications may interact with analgesics, altering their efficacy or increasing the risk of adverse effects. Considering concomitant medications is crucial in order to avoid unwanted interactions. Improving the quality of life for people who are experiencing pain requires good pain treatment. Pharmacological pain management techniques are a crucial part of pain management plans and should be used sparingly to minimize side effects and maximize pain reduction. An overview of the many pharmacological approaches to pain management is given in this article [17-27].

Adverse effects caused by opioids. ***Tolerance to pain.*** One of the main obstacles to the long-term use of opioids in clinical settings is the development of analgesic tolerance following repeated administration. One of the most popular and successful medications for treating severe pain is morphine. However, because of the possibility of side effects, such as analgesic tolerance, long-term morphine treatment is discouraged in the clinic. Reduced medication efficacy after repeated administration is a sign of tolerance. Dose increases are therefore necessary to sustain efficacy, which in turn leads to the development of cellular desensitization, tolerance, physical dependence, and behavioral withdrawal symptoms. Furthermore, rather than analgesic tolerance, greater morphine dosage is often needed because of accelerated disease development. Opioid rotation and the use of opioids in conjunction with

adjuvants are part of the clinical therapy of analgesic tolerance [7-13]. In individuals who need long-term analgesic treatment, adjuvants such gabapentin, pregabalin, dexamethasone, naproxen, ibuprofen, carbamazepine, aspirin, venlafaxine, and acetaminophen are used in conjunction with opioid analgesics. Similarly, to avoid antinociceptive tolerance, mixtures of opioid agonists and antagonists or opioids and non-opioid adjuvants are employed in preclinical research. GPCR kinases phosphorylate the opioid receptors when they are activated, which facilitates the binding with β-arr. Subsequent receptor internalization requires both phosphorylation and interaction with β-arr.It is possible for this internalized receptor to be broken down by proteases. Nevertheless, endosomes have the ability to recycle receptors and restore them to the cell membrane. In preclinical research, morphine and other opioids' antinociceptive effects are frequently quantified as either peripheral or central (brain and spinal cord) antinociception. While the hot-plate assay primarily assesses supraspinal-mediated nociception, the widely used tail-flick test may detect spinal-mediated nociception. In preclinical research involving repeated morphine therapy, one such antinociception test is typically carried out. Therefore, utilizing a different pain assay may result in a different evolution of antinociceptive tolerance [14-24].

Combining Therapies. A therapy approach called neuromodulation for pain uses chemical or electrical stimulation to change the nervous system's function and reduce pain. It focuses on long-term pain issues that have not improved with conventional therapies. Spinal Cord Stimulation (SCS) is a popular technique that involves implanting a tiny device close to the spinal cord to deliver electrical impulses that interfere with pain signals. In order to control aberrant neuronal activity linked to pain, deep brain stimulation (DBS) entails implanting electrodes in particular brain regions. Transcutaneous electrical nerve stimulation (TENS) blocks or lessens pain signals by delivering low-voltage electrical impulses close to the painful location using a portable device.109 Intrathecal drug delivery (IDD) delivers painkillers straight to the spinal cord using a pump. All things considered, neuromodulation for pain offers a different strategy by directly affecting the neurological pathways involved in pain perception, providing relief and enhanced functionality for people with chronic pain [20-25]. A range of strategies and methods that do not depend on drugs to reduce pain are included in non-pharmacological approaches for pain management. These methods seek to alleviate pain by using supplementary, psychological, or physical therapy. An explanation of every non-pharmacological pain management strategy [11,13,14].

Discussion. In the case of receptor homodimers or heterodimers, activation of one type of opioid receptor may have an impact on the behavior of another kind of opioid receptor in the same complex. Depending on the pharmacological characteristics of the ligands that interact with these receptors, two or more receptors might interact in different ways. According to recent research, the majority of opioid receptor ligands may bind to one or more off-target receptors to induce both desired therapeutic effects and undesirable side effects since they are not very selective. For instance, by activating the KOP receptor, morphine at high levels can cause analgesia in mice lacking the MOP receptor. Similarly, a DOP receptor agonist successfully induces analgesia in DOP receptor knockout mice, although naltrexone, a non-specific opioid antagonist, may counteract this effect. These findings have been taken as proof of the existence of a distinct DOP receptor subtype, despite the possibility that they represent non-specific interactions of the various DOP receptor agonists and antagonists [2,4,5,11]. Recent research, however, indicates that homo- or heteromeric receptor dimers may be present instead of opioid receptor subtypes. Given that MOP receptor deletion mice exhibit decreased DOP receptor activity. In order to treat moderate to severe acute and chronic pain, opioids are frequently employed. However, because they cause analgesic tolerance, addiction, and a variety of behavioral side effects that frequently lead to patient non-compliance, these kinds of analgesic medications have various potential drawbacks. Since opium and opioids have historically been used as analgesics, the precise processes underlying their negative side effects after prolonged usage are complex and poorly understood. Due to aging-related physiological changes and decreased metabolic capacity, older persons are more likely than younger adults to experience cancer and non-cancer chronic pain. As a result, they are more likely to experience adverse reactions to opioid medications [4-10]. Every opioid used in clinical practice is an agonist of the

μ-opioid receptor, and the main side effects are either directly or indirectly related to this receptor. Preclinical research suggests that peripherally limited opioids or multifunctional opioid ligands may cause less side effects, but more thorough clinical trials are needed to confirm these findings. In order to provide a better knowledge of the underlying pathophysiology and, eventually, to aid in the development of an appropriate therapeutic strategy to better control pain, the current review attempts to summarize the many pathways implicated in the deleterious effects generated by opioids [13-20]. All opioids, both clinically available and experimental, have certain negative side effects. However, the clinical use of opioids should be determined by the needs of specific patients and by calculating the drug's risk/benefit ratio. Furthermore, in order to effectively and safely treat pain, the complexity of chronic pain syndromes need customized pharmacological therapies and novel medications. In clinical trials, a number of experimental medications (such as opioids and ion channel inhibitors) can be used in conjunction with clinical opioids (such as intrathecal ziconotide, an N-type calcium ion channel inhibitor, and ω-conotoxins with intrathecal morphine) to provide better pain relief and fewer side effects than opioids alone. To control opioid-related side effects in clinical settings, more thorough research on the effectiveness of novel opioids or combination medicines is required [22-28].

Conclusions. In conclusion, common medications used to treat pain include opioids, nonsteroidal anti-inflammatory medicines (NSAIDs), antidepressants, and anticonvulsants. Although long-term use of opioids is linked to tolerance, dependence, and addiction, they are useful for treating acute pain. Although NSAIDs are useful in treating inflammatory pain, their usage is restricted due to the possibility of side effects such renal failure and gastrointestinal bleeding. Neuropathic pain is increasingly being treated with anticonvulsants and antidepressants, which have been shown to be effective in lowering pain intensity and enhancing function.

To balance the advantages and disadvantages of treatment, careful patient selection and dosage are required because these medications can have adverse effects. New drug targets and improvements in drug delivery systems are examples of emerging developments and future approaches in pharmacological pain management, opening the door to more efficient and individualized pain relief. Finding and creating new therapeutic targets to improve pain management has received more attention in recent years. This involves focusing on certain ion channels, receptors, or signaling pathways that are involved in the modulation and transmission of pain. To get the best possible pain relief and enhance quality of life, pharmacological pain management techniques should be applied sparingly and customized to each patient's needs.

New therapeutic targets and creative drug delivery methods are the main focus of emerging advances in pharmacological pain management. Researchers and pharmaceutical companies are working to create more effective, targeted, and customized painkillers by deepening our understanding of pain processes and applying cutting-edge technologies.

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