

The Field of Application of Analgesics and the Relevance of the Search for New Medicines

Iroda Takhirova Brodarovna ¹

Sokhib Rashidov Zamon o'g'li ²

Abstract: Acetaminophen is still one of the most widely used analgesics even though it has been on the market for more than a century. Additionally, acetaminophen has lately been used for multimodal analgesia in conjunction with non-steroidal anti-inflammatory medications, and its use, along with diclofenac and ibuprofen, dramatically surged during the 2019 coronavirus pandemic. Nevertheless, it is still unknown how exactly acetaminophen works as an analgesic. In this study, we compare the analgesic acetaminophen with diclofenac and ibuprofen while highlighting the existing mechanistic principles and thoroughly discussing the conventional, recognized, and hypothesized processes of acetaminophen. The selectivity of acetaminophen's cyclooxygenase inhibition for cyclooxygenase-2 is higher than that of ibuprofen but lower than that of diclofenac. The bulk of analgesics available to patients and prescribers are based on mechanistic classes of chemicals that have been known for a long time, despite extensive research into pain processes and substantial expenditure in research and development. With new formulations, delivery routes, and combination products, researchers continue to make the most of the mechanistic techniques available with a great deal of creativity and inventiveness. Here, we examine some of the mechanisms and modalities of analgesics that have recently been put into clinical development. This, along with improvements in our knowledge of the pathophysiology of chronic pain, should lead to the development of new treatments that could offer better pain relief to the many patients whose needs are still unmet. An overview of current research on pain biology, the application of preclinical models, and the creation of innovative pain treatments is what this study aims to deliver. Concerns about the advantages and disadvantages of the present analgesic development tactics are taken into consideration.

Keywords: Diclofenac, ibuprofen, cyclooxygenase, acetaminophen, analgesic, biotransformation, and mechanism

^{1,2} Department of Pharmacology of the Tashkent State Medical University

Introduction. Acetanilide was initially shown to have analgesic and antipyretic properties. But because of its severe side effects, less poisonous aniline derivatives were developed, and in the 1880s, phenacetin (4'-ethoxyacetanilide) and acetaminophen (4'-hydroxyacetanilide, also known as paracetamol) were synthesized. Phenacetin was discovered to induce hemolytic anemia, methemoglobin production, and kidney damage, despite being more widely used at first than acetaminophen. As a result, acetaminophen

overtook phenacetin as the most common over-the-counter and prescription medication for lowering temperature and pain. Acetaminophen is still one of the analgesics frequently used to treat both acute and chronic pain in the general population, despite the fact that it has been on the market for more than a century. Drug discovery and development continue to be a challenge, with increasingly high investments in R&D and increased numbers of submissions failing to translate into the delivery of novel chemical entities onto the market. The wide availability of generic and over-the-counter analgesics based on non-steroidal antiinflammatories (NSAIDs), acetaminophen, and “weak” opiates (and their combinations) provides many individuals with an accessible source of relief for mild to moderate pain [1-5]. However, many patients with chronic conditions such as osteoarthritis remain poorly treated. Opiates are still a useful option for treating moderate to severe pain, but they have a number of undesirable side effects, including constipation, nausea, vomiting, itching, and somnolence, as well as detrimental effects on patients' health, including poor sleep and difficulty concentrating, which can be so severe that treatment is stopped. In fact, according to a recent online study, individuals who use opiates for pain (as well as doctors who prescribe them) are willing to “trade-off” pain relief for a better tolerance profile, with 50% of patients and doctors stating that better side effects constitute the largest unmet need. Treatment for neuropathic pain is challenging due to its complicated pathogenesis. According to estimates, approximately one-third of patients are likely to experience 50% pain relief with monotherapy. For instance, in patients treated with pregabalin, the patient's global impression of change rating of much improved or very much improved was approximately 35% in cases of postherpetic neuralgia, 50% in cases of painful diabetic neuropathy, and 40% in cases of fibromyalgia [6-11]. A recent review found that published randomized, placebo-controlled trials in a variety of neuropathic pain populations had increased by 66% over the previous five years. It came to the conclusion that only a small improvement in pain relief had been made and that many patients continued to receive subpar care. Therefore, the challenge for drug discovery and development can be summed up as follows: we need to find analgesics that are safer, more effective at relieving pain, and have fewer adverse effects for a larger patient group. Nociceptive, inflammatory, and neuropathic pain are the three types of pain that are distinguished by the stimuli that cause them. Noxious stimuli produced peripherally cause nociceptive pain, proinflammatory mediators activate nociceptors in inflammatory tissues, and injury to the nervous system causes neuropathic pain. By influencing the enzymes, channels, and receptors involved in nociception and pain transmission, analgesics are thought to lessen these discomforts in both the peripheral and central nervous systems (CNS). The main goal of the current study was to concentrate on how acetaminophen and its related compounds interact with these biomolecules and to thoroughly discuss the conventional, acknowledged, and hypothesized mechanisms of analgesic acetaminophen, especially by highlighting the current mechanistic concepts and drawing comparisons with NSAIDs like ibuprofen and diclofenac [12-18].

The main purpose of this brief review presented is to analyze the scope of application of painkillers and the relevance of the search for new drugs based on the results of prestigious scientific research

There are several ways to relieve pain, but the mainstay of analgesic therapy is drug use. In recent years, there has been a significant increase in the clinical usage of analgesic medication combinations. Combining two or more medications with distinct modes of action is intended to create a synergistic interaction that will produce an adequate analgesic effect at lower dosages and, consequently, lessen the severity and frequency of side effects. Nowadays, a wide range of medication classes effectively supplement opioids or nonsteroidal anti-inflammatory medications (NSAIDs) in the treatment of pain. For the clinical treatment of both acute and chronic pain, opioids and NSAIDs have often been used together. Ultimately, using this combination restricts the amount of medication a patient can be given. Nevertheless, not every opioid-NSAID combination is always clinically effective. For instance, compared to acetaminophen alone, the combination of mild opioids like dextropropoxyphene with acetaminophen does not considerably improve pain relief. Similarly, codeine and paracetamol together provide more pain relief, but they may also make you feel more sleepy and lightheaded [4-11]. Therefore, in order to understand their potential clinical utility, a number of additional analgesic drug combinations need to be

assessed experimentally or clinically. We encourage researchers to submit both original and review articles that will support ongoing efforts to gather relevant data regarding the usage of medication combinations in pain management. Articles describing innovation models for clinical or experimental characterisation of medication combinations in the treatment of painful states, as well as fresh perspectives on the mechanisms behind drug interactions and the assessment of adverse reactions, are of special interest to us. Among the possible subjects include, but are not restricted to: Creation of mathematical models for medication interactions, Interactions between nonsteroidal anti-inflammatory medications and opioids or nonopioids, Animal models of drug interactions, Drug combinations in painful conditions in humans Pharmacodynamic and/or pharmacokinetic research on drug combinations in pain patients or animals, Drug combination-related adverse effects in pain patients, Combinations of medications and natural remedies in animals or pain patients [14-18].

Current approaches to the development of analgesics. Five major categories can be used to characterize the methods used to choose and move analgesics through development and onto the market. First, there are strategies intended to improve the safety or usefulness of currently available medications by creating new dosage forms or formulations. Examples include new extended-release or abuse-resistant versions of well-known medications like oxycodone, morphine, and tramadol; as well as alternative delivery systems like oral fentanyl lozenges and patches for the local administration of drugs like fentanyl, diclofenac, and lidocaine. Second, scientists have created substances that target established pathways, including those of opiates and NSAIDs. Third, combination products of already-existing chemicals have been created with the intention of enhancing effectiveness or minimizing undesirable side effects [1-4]. Oxycodone and ibuprofen combo products and naproxen with the proton pump inhibitor esomeprazole are two examples. Fourth, there are several instances where new analgesics have been created from recognized mechanistic classes of compounds or where the analgesic potential of medications initially created for other therapeutic indications has been identified and resulted in products specifically intended to treat pain. Celecoxib, rofecoxib, pregabalin, duloxetine, ropivacaine, and tapentadol are a few of them. Therapeutics arising from the discovery of novel mechanisms are the last and, for the most part, the minority. These include Sativex (GW Pharma), which works through a cannabinoid-based mechanism, and Prialt, an N-type calcium channel blocker. We conclude that more analgesics based on novel molecular mechanisms are required to address the unmet needs of patients in pain, while acknowledging the benefits of optimizing the utility of current medications and based on the unmistakable evidence that current medications have failed to deliver significantly improved benefits. Increased knowledge of the pathophysiological mechanisms behind pain and substantial investment in research and development to convert this understanding into new, safe, and effective analgesics are necessary for the discovery and development of such medications. Here, we outline some examples of new methods along with their mechanical background [5-11].

Behaviorally specified pain state mechanisms. Demonstrating convergence between the pharmacology that alters the observed behaviorally defined pain state and the underlying physiology of those systems that are activated by stimuli (which evoke the constellation of events defining a pain state) is the protocol for defining systems relevant to pain processing. Acute, intense mechanical or thermal stimulus. Populations of slow-conducting, unmyelinated (C) and mildly myelinated (A²) fibers are activated by acute, high-intensity heat or mechanical stimuli. Thermal or mechanical transduction channels, such as the TRP family of channels (TRPA1/TRPV1) or mechanically sensitive large cation channels, which are expressed in dorsal root ganglion (DRG) cells and small afferent terminals, determine the response characteristics of these afferents [5-10]. A variety of voltage-gated sodium channels, some of which are specific for tiny afferents (such as NaV 1.7, 1.8, and 1.9), mediate the conducted potentials that result from the depolarization of the C nociceptor. In order to mobilize populations of synaptic proteins (soluble N-ethylmaleimide-sensitive factor activating protein receptors [SNAREs]), this afferent traffic invades the central terminal and opens voltage-gated calcium channels of the N type (CaV2.2). As a result, synaptic vesicles containing and releasing a range of excitatory (glutamatergic and peptidergic) transmitters are deployed at the first order synapse. These transmitters acutely depolarize the second

order membrane by acting through the eponymous ionotropic (AMPA) and metabotropic (metabotropic glutamate receptor [mGluR]1 and 5; NK1) receptors. GABAergic and glycinergic interneurons regulate pre- and postsynaptic inhibition of the postsynaptic activation caused by big afferents projecting into the dorsal horn. When such inhibition is lost, postsynaptic activation that would otherwise be triggered by A β input is usually markedly enhanced, which in vivo results in a conspicuous tactile evoked pain behavior (such as allodynia) [11-18].

Discussion. Inadequate pain management has significant detrimental biological effects, such as cardiovascular pathology (hypertension, myocardial ischemia), suppression of gastrointestinal motility, suppression of spontaneous activity resulting in joint and muscle deterioration, and the physiological (loss of appetite, failure to thrive) and psychological effects of stress brought on by the aversive state. Economic indices and quality of life metrics clearly show the detrimental effects of pain. There are now a number of families of substances that have been shown to be clinically useful as painkillers. Their utility is frequently limited by their variable degrees of efficacy for the various pain states and associated adverse event patterns. Nonsteroidal anti-inflammatory medicines (NSAIDs), such as opiates and inhibitors of cyclooxygenases (COX-1 and/or COX-2), are commonly used to manage inflammatory conditions. Pain treatment has significant therapeutic implications for almost all medical specialties [1,2,3]. The organism's health suffers if its expression is not controlled. Understanding the intricate biology of the processes that underlie the processing of nociceptive information is crucial for the creation of innovative and effective treatments. Crucially, preclinical models have been very helpful in identifying the connection between the mechanism and the corresponding behaviorally characterized pain state. An overview of current research on pain biology, the application of preclinical models, and the creation of innovative pain treatments is what this study aims to deliver. Concerns about the advantages and disadvantages of the present analgesic development tactics are taken into consideration. Even with vigorous care, the patient's pain often persists to such an extent that the patient may still be qualified for admission into the original study, even though these drugs may have shown success. It is frequently challenging to determine whether the efficacy is constrained by a restricted role for the mechanisms addressed, a limitation of the drug target engagement, or whether the side effects prevent greater doses [5,7,8,9]. Thus, a lot of work and money has gone into developing new treatments to control pain. The complicated biology of pain processing and how it influences the creation of pharmacological targets for analgesic treatments will be discussed in this succinct introduction, followed by a remark on the screening of medications with analgesic therapeutic potential. It should be noted that the statement above is not exclusive to treatments for humans. It is becoming increasingly clear that treating companion animals' pain effectively poses significant therapeutic challenges, and the creation of efficient analgesics for that clinical population is a crucial goal in and of itself. Therefore, it should come as no surprise that changing one of these systems' components will likely have a significant impact on numerous other parts of the system's operation. It is noteworthy that a large number of medicines with established efficacy have a significant impact on afferent processing at the spinal level, where changes in the message caused by tissue and nerve damage are encoded [13-18].

Conclusions. It is obvious that the insights gained from combining molecular and physiological research with the role of the characterized systems in pain behavior provide a logical tool for developing analgesic targets and medications to engage these targets, even though there are obvious limitations and pitfalls in translating mechanisms defined in one species to another. This succinct overview highlights the intricacy of a system that is deeply ingrained in every facet of our biological system and has developed over millennia to encode the events that began with the duty of identifying fundamental risks to viability.

Therefore, it should come as no surprise that changing one of these systems' components will likely have a significant impact on many other parts of the system's operation. It is noteworthy that many of the medicines with established efficacy have a significant impact on afferent processing at the spinal level, where changes in the message caused by nerve and tissue damage are encoded.

Even with substantial funding for pain research, there are still several obstacles in the way of creating

innovative treatments. Without the addition of novel mechanisms to the analgesic arsenal, patients' demands for more effective pain management are unlikely to be satisfied. We hope to find high-confidence pain targets based on a solid understanding of mechanisms thanks to the emergence of exciting new technologies, the growing use of genetic approaches, and more funding for pain research. Drug discovery is still a very risky activity, though, and there are still many obstacles to overcome, including the time and expense of finding and developing the compounds and the methods for turning the research into medications that better serve the requirements of those who are in pain.

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