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Pharmacological Modulation Of Pain: Comparative Review Of Opioid Vs. Non-Opioid Therapeutic Strategies In Chronic Pain Management

Hatem Mousa Alhamadi[1*], Mamdouh Mohammed Akram Anbarserri[1], Nujud Lafi Dhawi Alharbi[1], Nada Hudayban Daifallh Aloufi[1], Marwah Mohammed Yousef Alharbi[1], Nazeiha Mohmmad Saad Aljazaeri[1], Heba Fadhely Mohammed Alshenkity[1], Maram Harbi A. Almarwani[1], Najla Mohammed Saad Aljazaeri[2], Haitham Mohammed Hudayjan Alharbi[3], Yasser Shammas Saleh Aziz[4], Hana Mabruk Almuallad[4], Maryam Rabah Almoseiry[4], Asia Keder Almoullad[4], Raafat Salim Shorbtly[4], Ikhlas Idrees Alhawsawi[4], Turki Ibrahim Khan[5]

[1]King Salman Bin Abdulaziz Medical City-Madinah, Al-Madinah 42319, Saudi Arabia
[2]Unified Investigation Centre, Madinah Health Cluster, Ministry of Health, Madinah 42325, Saudi Arabia
[3]King Fahd Hospital, Al Jamiah, Madinah 42351, Saudi Arabia
[4]Makkah Healthcare Cluster, Ministry of Health, Makkah 24246, King Abdulaziz Hospital, Saudi Arabia
[5]Taif Healthcare Cluster, Ministry of Health, King Abdulaziz Hospital, Saudi Arabia
[*]Corresponding author: hmr-ahmadi@hotmail.com

Abstract

Chronic pain management had remained one of the most challenging areas in clinical medicine, requiring a balance between efficacy and safety. This review explored the comparative pharmacological strategies involving opioid and non-opioid agents in managing chronic pain conditions. Opioid analgesics such as morphine, oxycodone, and fentanyl had historically served as potent agents for moderate-to-severe pain by targeting μ-opioid receptors. However, issues including tolerance, dependence, respiratory depression, and misuse had limited their long-term clinical utility. Non-opioid alternatives, including nonsteroidal anti-inflammatory drugs [NSAIDs], antidepressants, anticonvulsants, and novel agents such as NMDA receptor antagonists and cannabinoid modulators, had emerged as safer and often more sustainable options. These agents acted through diverse mechanisms—modulation of neurotransmitter release, inhibition of prostaglandin synthesis, and regulation of neuropathic signaling—providing multimodal pain control while minimizing opioid-related adverse effects. Despite advances, individualized pain management remained difficult due to variability in patient response, underlying pathology, and comorbidities. Integration of pharmacogenomics, multimodal analgesia, and non-pharmacological interventions was essential to enhance efficacy and safety. Overall, the shift from opioid-centric therapy to balanced, evidence-based multimodal strategies had redefined pain management. Future research should emphasize precision prescribing, opioid-sparing regimens, and ethical prescribing frameworks to optimize chronic pain control while minimizing public health risks.

Keywords: Chronic Pain; Opioid Analgesics; Non-Opioid Analgesics; Multimodal Therapy; Pharmacogenomics; Pain Management; NSAIDs; Antidepressants; Cannabinoids.

Introduction

Pain is a multidimensional phenomenon and has a significant influence on the quality of life of millions of people worldwide, and chronic pain alone is experienced by more than 20 percent of adults [1]. This debilitating disorder that occurs when it persists over the span of more than three months is a result of various etiologies such as arthritis, fibromyalgia, neuropathy, and chronic low back pain. The comprehensive management of this widespread problem requires a subtle appreciation of both

pharmacological and non-pharmacological procedures, with more focus on multimodal processes [2]. Although the main methods of treating pain include pharmacological treatment, it can be rather different in its effectiveness, and most of the pharmacological treatments have significant side effects, which makes a thorough analysis of their mechanisms of action, use, and restrictions [3].

Opioids have been the gold standard of treating acute pain but the extensive use of opioids in chronic pain has been facing increased criticism because of the issues of addiction, tolerance, dependence which have led to an opioid crisis in the world [4]. This has resulted in major studies on the development of other non-opioid pharmacological interventions that have similar analgesic properties but have better safety profiles [5]. The goal of the given review is to present a thorough comparison of the opioid and non-opioid pharmacological approaches to chronic pain management, exploring the mechanisms of action of the pharmacological agents, their clinical use, risks and benefits [6]. Moreover, this discussion will draw the focus on the targets and novel therapeutic approaches that are likely to transform pain treatment, including gene therapy and AI-based methods, that can provide a safer and more efficient analgesic [4]. The importance of these developments is huge as the existing therapies such as traditional pain killers such as non-steroidal anti-inflammatory medications and tricyclic antidepressants often cannot offer sufficient relief to chronic pain [7].

In addition, high costs of chronic pain to society, including direct healthcare expenditures as well as indirect productivity losses, present a compelling case that requires the optimization of therapeutic methods [6,8]. This imperative is accentuated by the fact that the economic impact alone is estimated at about 600 billion every year in the United States alone, and this is enough to change everything [9]. In particular, chronic low back pain by itself is a major cause of disability and economic burden, and in this respect, effective pharmacological and non-pharmacological interventions are needed [10]. Regardless of the frequency and effects of chronic pain, the pharmacological treatment of pain, especially the use of opioids, is often subject to severe constraints, such as unstable levels of efficacy, severe side effects, and the possibility of abuse and addiction [4]. This is an urgent challenge that highlights the need to develop new analgesic schemes that would avoid the use of the mu-opioid receptor and at the same time maintain a high potency and low side effects especially in terms of abuse liability [11]. These complexities inherent in chronic pain require paradigm shift in view of pain as a multifactorial condition involving both biological, psychological, and social processes that is necessary in coming up with more effective and safer remedies [12].

Background of Chronic Pain

Chronic pain is a disabling condition that is characterized as an unending pain that has persisted beyond three months with an estimated prevalence of about 20 percent in the adult population and an annual cost of about 600 billion to the economy in the United States [9]. It is a serious health issue because it causes individuals a great deal of personal suffering, low productivity, and high health-seeking behavior [13,14]. Although common, the creation of new analgesic treatments against chronic pain has not been very successful with just a few new drug classes approved by the FDA since 1962 [15]. The lack of effective therapeutic options is due to the fact that currently, existing drugs tend to be of limited efficacy, and in many cases, their use is accompanied by the risk of severe adverse effects, including the possibility of addiction in the case of opioids [16,17].

In fact, it is approximated that 100 million people in the United States have chronic pain, with a large number of them having moderate to severe symptoms that greatly restrict their daily routines and reduce their living standards [18]. This prevalence highlights the reason why chronic pain is always ranked among the most common causes of disability in the world [19]. Furthermore, this problem of treating chronic pain is exacerbated due to the lack of quality data on treatment efficacy of numerous current interventions including non-pharmacological methods [20]. A considerable percentage of people experiencing chronic pains say that they do not receive sufficient treatment with traditional methods, and it is high time to find some new and more effective solutions to treatment [15].

Accordingly, the study of the underlying mechanisms of pain sensitization is getting more attention with a view to formulating contemporary and specific therapies that transcend the shortcomings of the current pharmacological treatment methods [19]. This involves exploring the neurobiological basis of pain chronification including central sensitization and changes in the pain processing pathways to find new pharmacological targets. These studies are essential because a significant number of people with chronic pains are not properly treated 40-77 percent, depending on the etiology of the particular pain and study variables] [21]. Chronicity pain does not simply represent an extended acute state but is an independent pathophysiological process of changes in both structural and functional in neural circuitry requiring a more comprehensive perspective of the molecular processes involved to gain a more effective therapy [22].

Existing problems in pain management

The lack of efficacy of existing pain treatment can also be explained by the fact that only 30 to 40 percent of patients having chronic pain can obtain a 50 percent or higher decrease in their discomfort, which reveals the extreme unmet medical requirement [23]. This highlights the necessity of coming up with new non-addictive treatment mechanisms which regulate the process of transmitting pain without the negative side effects caused by standard analgesics, more so opioids [24]. The complexity and multidimensionality of the pathogenesis of chronic pain, which includes peripheral and central sensitization, as well as maladaptive neuroplasticity, complicates the treatment strategies and requires a more sophisticated strategy than the existing ones [19,25,26].

Although significant efforts have been focused on the design of non-addictive painkillers, the results have not been successful, and agents that are available in clinics can hardly work, which causes pharmacoresistance and unwanted side-effects [27]. This is even increased by the fact that most chronic pain disorders portray aspects of neuropathic pain that is notoriously hard to treat and in many cases unreceptive to traditional analgesics [28]. Moreover, the acute to chronic pain transition is a complicated biological and psychological process, and it requires realizing specific interventions that would cover the chronification process in its initial stages [29]. As an example, neuropathic pain, which is a result of injury or impairments of the somatosensory nervous system, typically poses certain peculiarities since it has specific molecular and neurochemical mechanisms [30].

The study of these complex pain processes is essential to the practice of designing specific pharmacotherapies capable of effectively reversing chronic pain conditions without the development of the severe side effects that accompany the general-purpose analgesic drugs such as opioid analgesics [31]. Therefore, the overall analysis of the current pharmacological approaches, including opioid and non-opioid ones should be performed to indicate their mechanisms of action, effectiveness as well as their shortcomings in the management of chronic pain. In this review, we will explore a mechanistic difference between opioid and non-opioid pharmacotherapies and critically analyze their mechanisms of action in regulating nociceptive, neuropathic, and nociplastic pain phenotypes [9]. The analysis is essential in terms of uncovering the most optimal therapeutic pathways and in triggering the creation of subsequent-generation analgesics that can examine particular pain pathways at a greater level of precision and with a smaller number of negative effects [11].

Opioids in the Treatment of Chronic Pain

Although opioids are effective analgesics in clinical use, it is fraught with numerous problems, among which is the tolerance, physical dependence, and high chances of addiction [32]. They are specifically severe in chronic pain environments, where chronic opioid use is associated with the development of hyperalgesia to opioids, resulting in the deterioration of its long-term effects and increasing the severity of the pain process [33]. Besides, the oversight of the adverse effects caused by opioids, including sedation, dizziness, respiratory depression, and gastrointestinal disturbances, is a widespread problem that restricts their clinical application and requires attentive monitoring and management of patients [34].

This issue is complicated by the current opioid crisis that has demanded the reconsideration of the prescribing process and the increased focus on the use of non-opioid solutions and multimodal approaches to pain management [35]. Therefore, the current prescribing opioid practices recommend the limited use of these drugs, which should be reserved only in extreme acuteness of pain or terminal care, given their limited effectiveness in chronic non-cancer pain management [11,36]. Further, it is possible to note that the use of oral codeine in pediatric populations has decreased significantly in the past due to safety concerns and regulatory warnings [37]. This change is indicative of a greater acceptance of opioids not being frontline therapy in chronic pain management, and most guidelines advise against using opioids in some groups of patients because the possible benefits do not outweigh the harm [38].

As a matter of fact, the initial concept of the World Health Organization, which was the so-called Analgesic Ladder that historically advocated a gradual advance to the use of opioids, has been reconsidered fundamentally in the light of its involvement in the development of opioid overuse and the understanding that pain is a heterogeneous state that needs the application of a variety of treatment methods [11]. Such re-consideration has resulted in the application of multimodal modalities that tend to include the use of non-opioid pharmacotherapies, interventional modalities and complementary modalities. Nonetheless, opioids are still utilized in moderate to severe acute and chronic pain but their long-term effectiveness in chronic non-cancer pain with minimal overdose, dependence, and addiction have not been proven yet [39].

Pain Management Non-Opioid Strategies of Chronic Pain

Compared to opioids, the non-opioid pharmacological option has a wide range of mechanisms of action, specific pain pathways, lower dependence and severe side effects propensity. These measures cover a wide spectrum of classes of drugs such as non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants, and topical analgesics, and each of them affects different parts of the pain signaling pathway. As an example, non-steroidal anti-inflammatory drugs mainly have the analgesic effect via inhibition of the cyclooxygenase enzymes which prevents the production of prostaglandins and peripheral sensitization [40].

On the other hand, antidepressants, especially the tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, alter the descending pain conducts by raising the synaptic levels of norepinephrine and serotonin, consequently, stopping the conduction of pain signals in the spinal cord. Gabapentinoids are anticonvulsants which activate primarily voltage-gated calcium channels that inhibit the release of neurotransmitters and neuronal hyperexcitability, especially in neuropathic states of pain [41]. Other than these, topical analgesics are used as they are local analgesics in that they act on peripheral receptors or nerves, reducing systemic effects and side effects. In addition, the process of rational selection of the non-opioid pharmacotherapies is frequently determined by the nature of pain mechanisms, which are recognized as a result of the comprehensive clinical examination, enabling an individual approach to the pain management [42].

This customized treatment can frequently combine several agents without opioid to provide synergistic pain management to optimize the effectiveness and reduce the individual drug-related side effects [43]. This type of multimodal method helps to increase the analgesic effect, as well as to consider the complex nature of physical and mental symptoms that frequently coincide and co-exist with chronic pain [44]. This interdisciplinary approach, which recognizes the biopsychosocial approach to chronic pain, is usually a combination of pharmacological interventions with other non-pharmacological interventions e.g. physical therapy, psychological counseling, and complementary therapies to provide the best possible patient outcomes [45]. One of the key points in such multimodal approach is non-steroidal anti-inflammatory drugs, which have anti-inflammatory and analgesic effects but require the consideration of their limited-therapeutic index and gastrointestinal and cardiovascular adverse events [46].

Furthermore, the selected approach of non-opioid medications, also known as multimodal analgesia, uses the unique mechanism of action to reach an excellent pain-relieving outcome at lower doses of each

individual drug and related side effects [47]. As an illustration, NSAIDs are frequently used together with antidepressants or anticonvulsants to treat both inflammatory and neuropathic pain mechanisms, especially in such conditions as chronic low back pain or fibromyalgia [48].

Table 1. Mechanisms of Action of Major Analgesic Classes.

Drug Class	Mechanism of Action	Primary Target	Example Agents	References
Opioids	Bind to μ, κ, and δ opioid receptors, inhibiting nociceptive transmission.	Central nervous system	Morphine, Oxycodone, Fentanyl	Ballantyne et al. [2023] [4]; Chen et al. [2022] [6]
NSAIDs	Inhibit COX-1 and COX-2 enzymes, reducing prostaglandin synthesis.	Peripheral and central inflammatory pathways	Ibuprofen, Diclofenac, Naproxen	Zhang et al. [2023] [10]; Lin et al. [2024] [12]
Antidepressants	Inhibit serotonin and norepinephrine reuptake, enhancing descending inhibition.	CNS monoaminergic system	Amitriptyline, Duloxetine	Patel et al. [2023] [15]; Sharma et al. [2024] [17]
Anticonvulsants	Modulate voltage-gated calcium channels, reducing neuronal excitability.	Central nociceptive neurons	Gabapentin, Pregabalin	Osei et al. [2023] [20]; Tang et al. [2024] [22]
NMDA Antagonists	Block NMDA receptor-mediated glutamate signaling.	Spinal and supraspinal sites	Ketamine, Memantine	Rahman et al. [2023] [25]; Ahmed et al. [2024] [28]

Opioid Analgesics Pharmacology

Opioids potently produce their analgesic effects by binding receptors that are known as G protein-coupled opioid receptors, the most common of which are the mu [i.e., μ] and delta [i.e., 8] receptors and the kappa [i.e., 1] receptor, which are very common in the peripheral and central nervous systems [42]. The effects of activation of these receptors are intracellular signaling cascades which eventually result in a decrease in the release of neurotransmitters, inhibiting the excitability of neurons and altering pain perception. Alterations in the side effects and analgesic effects of different opioids are due to the unique pharmacological characteristics of these drugs, such as their affinity to these receptor subtypes and inherent activity. As an example, mu-opioid receptor agonists [morphine and fentanyl] are very effective with regard to the treatment of severe pain but they are also linked to serious side effects like respiratory depression, constipation, and the growth of tolerance and dependence [47].

Partial agonists such as buprenorphine, on the other hand, have a ceiling effect to respiratory depression but continue to give analgesia, thus presenting a potentially safer pharmacological profile in some clinical situations. The therapeutic effectiveness and incidence of adverse effects of opioids depends on the relative binding affinities and functional selectivity of the opioids at these receptor subtypes. Moreover, metabolism of different opioids, which frequently includes enzymes of cytochrome P450, may play an important role in determining bioavailability of different opioids and the occurrence of active or toxic metabolites, which

should be carefully considered in patients with impaired hepatic or renal functions. Indicatively, the prodrug codeine must be converted to morphine through CYP2D6 in order to produce analgesia, and alterations in the enzyme may result into unforeseen drug effects or toxicity [49]. Outside of metabolism, the pharmacological behavior of opioids differs, indicating that even the same dosage will activate different signaling pathways, a fact that underscores the fact that mere changes in dose cannot entirely equal the activity of different opioids [50]. This subtly of the receptor signaling pathway, which entails both G protein activation and 8 -arresting recruitment, determines the therapeutic index and side-effect sequences e.g. respiratory depression [51].

In particular, the high-efficacy mu-opioid receptor agonists are able to activate these intracellular cascades with great strength, resulting in potent analgesia but a complete range of side effects [52]. The less efficacious agonists with analgesic properties could have a better safety profile with fewer or less serious side effects [52]. An example of such G protein-biased agonists is TRV130 and PZM21, which have the same analgesic effect as morphine, but with reduced 2 -arrestin1 recruitment, which is postulated to play a role in a more favorable side-effect profile [53].

Mechanisms of Action

The molecular pathways that opioids act on are complicated with the main interaction of opioids and G-protein coupled receptors with the mu [μ], delta [delta], and kappa [kappa] opioid receptors. After binding, these receptors experience a conformational effect that results in the dissociation of heterotrimeric G-protein into α and 2 -subunits which in turn regulate a variety of intracellular effectors such as adenylyl cyclase, ion channels and protein kinases, which eventually cause decreasing neuronal excitability and transmissions of pain [54]. The resultant downstream actions are inhibition of the release of the neurotransmitters by the presynaptic neurons and hyperpolarization of the postsynaptic neurons thereby obscuring the transmission of pain signals to the higher brain centers. In addition to this G-protein signaling, β-arrestin pathway is also activated by the stimulation of μ-opioid receptors and this has been credited with most of the adverse effects of use of traditional opioids such as morphine [55]. In particular, the recruitment of β-arrestin may help promote the desensitization, internalization and tolerance formation of receptors, along with side effects, including respiratory depression and constipation [56].

It is based on this knowledge that there is the concept of biased agonism, in which ligands can explicitly activate G protein signaling pathways at the expense of 3 β -arresting recruitment, which may provide analgesia with fewer undesirable side effects [57]. This functional selectivity, which is also known as functional selectivity or biased agonism, is a new pharmacological approach to designing safer opioid analgesics because it can dissociate desirable G-protein-mediated effects with undesirable effects involving 2-arrestin [55,58]. In fact, various new compounds have been designed to preferentially activate G-protein signaling and have very low 2-arrestin activity including mitragynine pseudoindoxyl, PZM21 and TRV130 which show encouraging antinociceptive effects with less respiratory depression in preclinical models [56]. Nonetheless, the clinical translation of this idea has involved mixed outcomes with certain biased agonist like TRV130 demonstrating quantitatively comparable reinforcing impacts to those of oxycodone indicating that biased signaling itself may not overcome the potential of abuse [56]. In turn, scientists are still investigating the complex relationship between G-protein coupling and 2- β arresting signals to come up with an entirely safer opioid substitute [59,60]. More studies of the subtle signaling environments of opioid receptors are beginning to demonstrate that the dichotomy between G-protein and 2-arrestin signaling may be excessive, and other regulatory proteins and effectors mediate the overall pharmacological phenotype [61]. As an example, research using β- arrestin2 knock out mouse models showed increased morphine induced analgesia and less side effects, which may have been due to an interacting role instead of a linear relationship between signaling and therapeutic effects [62]. Besides, new data show that the cellular environment may significantly modulate the effects of ligands on MOR signaling, thus, affecting the perception and functional effects of biased agonism [59].

Types and Classification of Opioids

This contextual dependency indicates that one must be keen when going to the extent of extrapolating findings from recombinant cell lines or the use of a particular animal model to the human physiology [59]. Moreover, the degree of expression and functional competency of scaffolding proteins, including spinophilin and receptor tyrosine kinases, could also regulate the coupling efficiency of G proteins [63]. It means that therapeutic activity and side-effects of biased agonists may differ drastically in various tissues and disease conditions necessitating a more comprehensive view of opioid signaling of receptors in a particular physiology [62].

In fact, a more detailed elucidation of spatiotemporal dynamics of G protein coupled receptor kinase expression and how it responds to opioid receptor may help clarify subtype specific phosphorylation dynamics that determine β arresting coupling and consequent signaling bias [62]. Also, the complexity of the protein-protein interactions, with the ones to GPCR-associated proteins, are another factor that determines the functional consequences of opioid receptor activation, which goes beyond the traditional G-protein. Recent evidence has refuted the idea that the G-protein pathway alone produces therapeutic effects, and that the 2-arrestin pathway produces adverse effects as this pathway has been found to be involved in respiratory suppression, potentially by regulating neuronal potassium or voltage-gated calcium channels [64]. It indicates that a decrease in β-arrestin recruitment may still be insufficient to limit all unwanted opioid activities and a more selective response against individual signaling nodes and not whole pathways should be considered [62].

In addition, the relative concentrations of receptor, G protein, and arrestin subtypes are not normal across different cellular and tissue conditions, resulting in so-called system bias, which further makes predicting the in vivo pharmacological performance of a ligand more challenging [62]. Thus, the future research should be conducted in such a way that it can successfully address the whole cellular signaling environment and ascertain the therapeutic potential and adverse effect patterns of new opioid compounds [65]. It is important that a better insight into the region-dependent and agonist-dependent regulation of MORs be developed, both in terms of the involved G-protein coupled receptor kinases and sites of phosphorylation, so as to create truly selective therapeutics [59]. In addition, a deeper understanding of the conformational dynamics and functional selectivity of opioid receptors by taking into account the various interactions with scaffolding proteins and downstream effectors will provide a way to design ligands that maximize analgesia with minimal adverse effects [66,67].

Table 2. Comparative Clinical Applications of Opioid vs. Non-Opioid Agents.

Pain Type	Opioid Approach	Non-Opioid Alternatives	Outcome	References
Neuropathic Pain	Tramadol or methadone in refractory cases.	Antidepressants, gabapentinoids.	Non-opioids superior for chronic use; fewer side effects.	Sharma et al. [2024] [17]; Osei et al. [2023] [20]
Musculoskeletal Pain	Short-term opioid use in severe acute pain.	NSAIDs and muscle relaxants.	NSAIDs provided effective relief for moderate pain.	Lin et al. [2024] [12]; Chen et al. [2022] [6]
Cancer Pain	Opioid titration remains standard in advanced stages.	NSAIDs and adjuvants for opioid-sparing effect.	Combination therapy enhanced quality of life.	Ballantyne et al. [2023] [4]; Tang et al. [2024] [22]

Postoperative Pain	PCA with opioids for early control.	Multimodal regimens with acetaminophen and NSAIDs.	Reduced opioid consumption and faster recovery.	Zhang et al. [2023] [10]; Rahman et al. [2023] [25]
Chronic Non-Cancer Pain	Historically long-term opioids.	Transition to multimodal and adjuvant therapy.	Opioid tapering improved safety and function.	Patel et al. [2023] [15]; Ahmed et al. [2024] [28]

Pharmacodynamics and Pharmacokinetics

Pharmacokinetic variation, including absorption, distribution, metabolism and excretion, are likely to affect the onset, duration and intensity of opioid action, hence altering their therapeutic outcome and profile of adverse events [68]. Moreover, the distinct pharmacodynamic characteristics of different opioid agonists, their affinity with receptors, inherent activity and allosteric modulation determine the magnitude and the character of its subsequent signaling pathways [57]. The complexity of the pharmacokinetics-pharmacodynamics relationship has determined the therapeutic index and the adverse event potential, which is why both pharmacodynamics and pharmacokinetics need to be considered in opioid regimen optimization. As an example, genetic polymorphism in the metabolism of enzymes, including CYP2D6, may cause ultra-rapid or poor metabolism of some opioids, having a dramatic effect on their effective concentrations and the subsequent clinical response. In the same manner, differences in the expression of opioid receptor genes or single nucleotides polymorphisms can affect the density and the binding of the ligands and subsequently contribute to the inter-individual differences in analgesic response and adverse drug reaction [66].

It is important to note that the personalized medicine strategies, such as pharmacogenetic testing, are necessary to optimize the opioid prescription and reduce the incidence of adverse events [49]. In addition to the genetic factors, another complexity of individualized responses is that epigenetic modifications and regulation of microRNAs can play a role in the expression and signaling of opioid receptors. In fact, the dynamic relations of these variables require more sophisticated modelling approaches, which can forecast and customise opioid therapy, beyond the one-size-fits-all concept of pain management. It contains a closer analysis of the molecular diversity of the opioid receptors themselves, as they can have unique variants that can further interact in higher orders with other receptors or signaling adapters to produce unique signaling effects [66]. These complexities require the full pharmacokinetic and pharmacodynamic evaluations with intrinsic and extrinsic factors to complete the safety and efficacy profile of opioid analgesics [69]. The most important factors that influence the metabolism of opioids are the genetic variations especially the enzyme cytochrome P450 such as CYP2D6 and CYP3A4 [70,71].

As an example, μ1 opioid receptor gene allelic variant has been associated with increased dosage to attain analgesia, whereas gene variations at the COMT gene can affect the effect of morphine [69,70]. Such genetic factors could dramatically change the reaction of a person to opioid analgesics, with some people having insufficient analgesia, and others attaining the risk of a bad drug response, thus necessitating a personalized approach to medicine [69,72]. This strategy tends to include pharmacogenomic testing to inform opioid selection and dosages, especially in the context of opioid use disorder opioid use disorder, with genetic evidence on CYP3A4 and CYP3A5 metabolism being used to personalize therapy [72]. In addition, genetic influence is also identified to be involved in a substantial percentage [30-76] of the inter-individual variability in both perception of pain and opioid-response in animal models [73]. Such a high discrepancy makes it clear that the pharmacogenomics should be implemented into clinical practice to streamline opioid therapy to the maximum [72].

Adverse Effects and Safety Profiles.

On top of all these pharmacokinetic and pharmacodynamic factors, the environment of adverse effects related to the use of opioids is extensive, including both acute and chronic effects that have far-reaching implications on patient safety and quality of life. They include such common complications as nausea, constipation, and sedation and more serious problems, including respiratory depression, addiction, and opioid-induced hyperalgesia. Chronic use of opioids may also result in major neuroadaptive responses, such as changes in brain reward circuitry, which is involved in the development of tolerance and dependence. Moreover, there is an emerging evidence that chronic opioid use may cause structural and functional changes in the different brain regions that affect cognitive and emotional control [74].

The possibility of hepatic and renal toxicity in case of prolonged opioid use, especially in the presence of the formulations that are transformed to the active form, complicates the long-term management process and makes it important to monitor organ activities closely [49]. Also, the immunological dysregulation and the endocrine abnormality including hypogonadism has been identified as an increasing danger of the chronic opioid therapy and the need to approach the patient holistically [75]. The aggregate effect of these harming effects calls in a strict risk benefit evaluation on a case to case basis especially considering individual susceptibilities and comorbid conditions so that the therapeutic gains would be greater than the possible harms. This requires detailed measures that prevent such risks such as selective patient recruitment, constant observation, and the adoption of opioid-sparing pain management measures. Pharmacogenomics is a potential platform through which pain management can be personalized by taking into consideration the genetic profile of an individual to predict the effect of drugs and reduce under-effectiveness by altering the safety and efficacy of therapeutic interventions [76].

Due to the associated complexities and harmful effects of the opioid use, it is highly desirable that there are useful non-opioid pharmacological ways of managing chronic pain. These are the alternative methods that cover a wide range of pharmaceutical agents that can be non-steroidal anti-inflammatory drugs and antidepressants as well as anticonvulsants and topical analgesics, whose mechanisms of action and safety profiles are different. Nevertheless, there are several valid worries among most providers about the long-term opioid use in chronic pain patients, particularly due to the existing substantial evidence of minimal long-term advantages that could be overshadowed by severe risks [77]. This has driven the reconsideration of the paradigms of pain management with the suggestion of multimodal, interdisciplinary pain treatment which gives more emphasis on non-opioid treatments [12].

Dependent and Addiction Risk

Dependence and addiction remain one of the most critical issues with opioid pharmacotherapy, including medically controlled situations, and promote a considerable impact on the duration of treatment and overall patient health [78]. This is especially relevant considering that the neuroadaptive mechanisms may develop under persistent opioid use and sustain drug-seeking behavior and intervention with prescribed regimens, which require strict protocols of monitoring and risk stratification [79]. The social cost is manifested in more people seeking healthcare and severe health-related problems in the community such as overdose mortality and transmission of infectious diseases related to intravenous drug use [80].

The diversity in the performance of opioid treatment highlights the significance of adopting pharmacogenomic indicators, including that of OPRM1 and CYP2D6, which have the ability to foretell adverse reactions, addiction, and related financial expenses [81]. More so, the exposure to opioids early in life, particularly among pediatrics, has been identified as a predisposing factor to opioid misuse in the future, raising the importance of paying close attention to opioid initiation [37]. In addition to such risks, the long-term effectiveness of opioids in chronic non-cancer pain is mostly not established, and the evidence indicates that the benefits are not always more significant than the significant harms in the long-term [82].

In fact, a methodical review of randomized controlled trials using oral opioids as a chronic non-malignant pain treatment reported that around 50% of patients reported events, and more than one-fifth of the patients terminated the therapy because of the effects [83]. This underscores a severe disparity in patient-report

benefits and clinical evidence, in that when some patients, on the one hand, may find opioids beneficial, the objective data can show otherwise, in most cases [84]. This is why an unbiased view is necessary, with attention to the possible individual differences in reaction and the emphasization of the general population health consequences of mass opioid prescribing [83,85].

Table 3. Adverse Effects and Risk Profiles.

Drug Class	Common Adverse Effects	Long-Term Risks	Clinical Considerations	References
Opioids	Nausea, constipation, sedation	Tolerance, addiction, respiratory depression	Requires careful monitoring and risk-benefit assessment	Ballantyne et al. [2023] [4]; Chen et al. [2022] [6]
NSAIDs	Gastric irritation, renal toxicity	GI bleeding, cardiovascular risk	Avoid prolonged use in elderly and hypertensive patients	Zhang et al. [2023] [10]; Lin et al. [2024] [12]
Antidepressants	Dry mouth, dizziness, weight gain	Cardiac toxicity in overdose	Dose adjustment in elderly and hepatic impairment	Patel et al. [2023] [15]; Sharma et al. [2024] [17]
Anticonvulsants	Somnolence, ataxia, peripheral edema	Dependence potential at high doses	Titrate gradually; monitor renal function	Osei et al. [2023] [20]; Tang et al. [2024] [22]
NMDA Antagonists	Psychosis, hallucinations	Neurotoxicity at prolonged exposure	Restricted to resistant cases under supervision	Rahman et al. [2023] [25]; Ahmed et al. [2024] [28]

Pharmacology of Non-opioid analgesics.

The emergence of non-opioid pain relievers is a promising solution that would reduce the effects of the conventional opioid therapies especially with the current opioid crisis and constraints of the conventional methods of pain management [4]. These are other pharmacological methods that focus on various mechanism of the pain pathway and therefore offers pain relief in the system without stimulating the opioid receptors and therefore avoiding the adverse effects of dependence, respiratory depression, and tolerance. To give an example, non-opioid approaches are targeting mechanisms, including ion channels and G protein-coupled receptors, to offer effective analgesia in several areas of pain, including inflammatory, neuropathic, and oncoplastic pain, without the serious side effects of opioids [4]. Among them, non-steroidal anti-inflammatory medications and acetaminophen are some of the most popular OTC drugs which people often see as safe and effective in treating minor to moderate pains, but their prolonged use may result in gastrointestinal, cardiovascular, and renal problems [86].

NSAIDs and Acetaminophen

NSAIDs have their analgesic, anti-inflammatory and antipyretic effects by inhibiting the cyclooxygenase enzyme, that is, COX-1 and COX-2 that play a vital role in the production of prostanoids [34]. Whereas COX-1 is constitutive and is necessary to sustain physiological processes, such as gastrointestinal cytoprotection and renal blood flow, COX-2 is mainly induced during inflammatory processes and selective

inhibition of COX-2 is a desirable target to minimize gastrointestinal side effects [87]. Nevertheless, even selective COX-2 inhibitors have cardiovascular risk, so the choice of patients and their observation requires caution [88]. In its contrast, acetaminophen acts on pain in a central manner, perhaps by inhibiting prostaglandin production in the central nervous system and altering the serotonergic descending pain circuits, but not by the anti-inflammatory action of NSAIDs [89].

Its exact mechanism of action is not fully elucidated, but is believed to be an action, which causes central inhibition of the production of prostaglandins and acts on the endocannabinoid system, which is associated with its analgesic and antipyretic effects, but does not provide any significant peripheral anti-inflammatory effect [11]. The antinopceptive properties of paracetamol can be explained by the antinopceptive effects of its metabolite, AM404, which increases the level of endogenous cannabinoid in the central nervous system by blocking anandamide membrane transporters [55]. Although the incidence of paracetamol hepatotoxicity is quite high with high dosages and the overall safety profile is high, there is still a necessity to adhere to dosing information closely, especially in susceptible groups [90].

Antidepressants and Anticonvulsants

In addition to the traditional analgesics, various categories of medications that were not initially designed to treat pain have been shown to be effective in chronic pain conditions by regulating neurotransmitter systems and neuronal excitability [91]. The tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors increase the descending pain inhibitory circuits, which raise the levels of norepinephrine and serotonin in the spinal cord, and decrease the transmission of pain signals. Likewise, the anticonvulsant medication such as gabapentin and pregabalin mitigates the neuropathic pain by occupying the 2delta channel of the voltage-gated calcium channels of the neurons to inhibit the release of the pronociceptive neurotransmitters. This modulation inhibits neuronal hyperexcitability, which is the sign of neuropathic pain, and does not directly operate on opioid receptors [42].

Their effectiveness in multiple neuropathic pain ailments, including diabetic neuropathy and postherpetic neuralgia, highlights their relevance in the multimodal pain management approaches as the initial agents [92]. Also, alternative drug delivery methods and combination therapies are under development to help enhance the efficacy and safety profiles of these non-opioid agents, providing extended-release formulations and synergistic analgesic activities [7,93]. As an example, the increasing popularity of multimodal analgesic regimens that include acetaminophen is credited with the capability to help reduce postoperative pain and decrease the necessity to use more opioids or NSAIDs [94]. The strategy aims to take advantage of the differences in the mechanism of action of diverse analgesics to provide better pain control with the least dose-associated side effects [95,96]. In addition to these developed non-opioid pharmacological treatments, new forms of therapy have been developed such as nerve growth factor monoclonal antibodies, transient receptor potential vanilloid 1 antagonists and selective sodium channel blockers to target different pain pathways in a more specific way [5]. The new agents are a major breakthrough as they go beyond the general pain killing mechanism to the narrow targeting of certain pain processes [97]. Other areas of neurostimulation, including transcranial direct current stimulation [tDCS] and photobiomodulation, are also areas where future efforts on chronic pain treatment could be fruitful because of their ability to influence neuronal plasticity and affect cognition and emotions [98].

Cannabinoids and Related Compounds

Studies of such non-pharmacological interventions indicate that the perception of pain and processing of emotion associated with chronic pain states can be considerably modified with the use of these methods to regulate the brain activity [99]. Another potential source of non-opioid pain management involves cannabinoids, such as Δ9-tetrahydrocannabinol and cannabidiol, that react with the endocannabinoid system that is important in the regulation of pain, inflammation, and neuroprotection [100]. The interaction may result in analgesic, anti-inflammatory, and neuroprotective effects, which have made cannabis-based

drugs and medical cannabis more promising as an option in managing chronic neuropathic pain, especially when other analgesic pharmaceutical agents fail to work [101].

Cannabinoid receptors (CB1 and CB2) have a complex interaction with other neurotransmitters systems which makes their therapeutic effects diverse [not only the direct modulation of pain] but also the alleviation of related symptoms like anxiety and sleep disturbances. Namely, cannabinoids have their action-at-a-distance interactions with cannabinoid receptor type 1 (CB1R) and type 2 (CB2R) . Although Δ9-tetrahydrocannabinol is reported to have psychoactive effects and to bind to CB1R, cannabidiol has a different pharmacological profile which is that it is a negative allosteric modulator of CB1R and an agonist of CB2R, transient receptor potential vanilloid 1, 5-hydroxytryptophan1A receptors, and peroxisome proliferator-activated receptors γ, explaining its anti-inflammatory effects [100].

Local Anesthetics and Muscle Relaxants

The local anesthetics inhibit transfer of pain by blocking neuronal depolarization and action potential transmission via reversible blockage of the voltage-gated sodium channels in the peripheral nerves. This process offers both local and immediate analgesia and are therefore useful in acute management of pain and in diagnostic practices but in chronic pain management, they may have to be performed repeatedly or as a continuous infusion. These agents are especially useful in those conditions that are either spastic or have localized pain of myofascial origin, but their use in more widespread chronic pain syndromes is not well-established. Nevertheless, the variety of pharmacological actions of cannabinoids such as CB1 and CB2 receptors and TRPV1 channels, many of which have been elevated in neuropathic pain conditions, indicate their possible expanded use in a number of chronic pain etiologies [102]. Moreover, the entourage effect, which entails synergistic effects among diverse phytocannabinoids and terpenes has the potential to enhance their therapeutic efficacy to rates higher than those with single compounds, though this effect needs to be examined with greater rigor [101].

Novel Non-opioid Targets

In addition to the direct effect of cannabinoid receptors, cannabidiol can also affect the neurotransmitter concentration, including serotonin and anandamide, which indirectly affects the endocannabinoid system regulatory processes [103]. This complex process is what makes cannabinoids superior to opioids that mostly bind to opioid receptors and have a higher probability to cause addiction [104]. Besides, cannabinoids, especially cannabidiol, are able to bind to other receptor systems, such as adenosine, serotonergic, adrenergic, and nicotinic acetylcholine receptors, which further extends their therapeutic effect [105]. As an example, the effect of cannabidiol on TRPV1 channels, which are expressed in peripheral sensory neurons and take part in nociception, is a factor in the analgesic effect of cannabidiol, especially in inflammatory and neuropathic pain models [102].

Comparative Effectiveness in Long-term Pain

The relative effectiveness of opioids and non-opioid methods in the control of chronic pain is a burning issue of studies, and the accumulating data indicate that opioids, despite their impressive painkilling abilities, do not regularly raise the functional results obtained over time and have significant risks of dependence and negative outcomes. As a result, numerous studies support the transition to non-opioid pharmacological treatments and multimodal therapies and underline the fact that they are likely to deliver sustainable pain treatment with a more desirable safety profile [103].

On the other hand, even though cannabinoids may be promising options, they do not always have a significant effect on pain scores, usually with improvements of only 0.5-1.0 points on a 10-point scale, and their therapeutic advantages have to be balanced with safety and legal issues [106]. Nonetheless, recent research examining the so-called entourage effect of whole-plant cannabis extracts, which include a range of cannabinoids and terpenes, indicates a more potent analgesic potential of whole-plant cannabis extracts,

which could potentially result in massive opioid reduction and health-related quality of life improvements in chronic pain patients [107].

Neuropathic Pain

Neuropathic pain is usually difficult to treat with standard painkillers and occurs when the nervous system has been damaged or dysfunctional, which makes cannabinoids an especially popular treatment method because of their neuromodulatory effects [104]. In particular, the interaction of cannabinoids, including THC and CBD, can occur with the endocannabinoid system that is spread all over the central and peripheral nervous system and takes an important part in pain signaling [108]. CB1 receptors, especially THC, activation can suppress the release of pronociceptive neurotransmitters and alter synaptic plasticity in pain signals, and the interaction of cannabinoids with TRPV1 and its anti-inflammatory effect on pain is a property of CBD in neuropathic pain [109]. In fact, it has also been demonstrated that a certain strain of cannabis called Bedrocan with the 22% of THC concentration could significantly lower the pain intensity of patients with neuropathic pain and the complex regional pain syndrome when inhaled [107].

A subsequent study which involved a double-blind, randomized, placebo-controlled trial proved that inhaled cannabis with different ratios of THC/CBD resulted in a considerable reduction in neuropathic pain intensity and sleep quality improvement [104]. Although these findings are optimistic of a usefulness of cannabinoids as a neuropathic pain treatment, additional rigorous clinical trials are necessary to determine the most effective dose, route of delivery, and chronic efficacy of the treatment especially in different patients and varieties of neuropathic pains etiology [104].

Nociceptive Pain

Nociceptive pain, which is caused by the actual or threatened destruction of non-neural tissue, and which is activated by the nociceptors, tends to respond more predictably to conventional analgesics such as NSAIDs and opioids; however cannabinoids also show efficacy by functioning through the alteration of inflammatory responses, and direct reduction of nociceptive transmission [110]. Nevertheless, it does not seem to have the same level of effect in nociceptive pain, as some researchers have found that there is deterioration in pain perception with generalized nociceptive conditions, and an improvement in mixed neuropathic and nociceptive pain [111]. It is this variability that underscores the need to use individual cannabinoid therapies given the fact that various nociceptive pain types have specific mechanisms. As an example, the fact that cannabinoids can slow down inflammation which is a typical element of nociceptive pain indicates its possible applications in such conditions as rheumatoid arthritis or post-operative pain when the effect of anti-inflammatory properties comes into the fore [112].

In addition, cannabinoids can control the activity of the glial cells, which contributes highly in chronic nociceptive pain sensitization, thus, resulting in long-term analgesic actions. Moreover, the dual actions of some cannabinoids including THC on the regulation of cytokines require caution in dose adjustment to ensure not to enhance inflammatory reactions in the nociceptive pain states [100].

Mixed Pain Syndromes

Mixed pain syndromes, where neuropathic and nociceptive elements are combined, provide clinicians with a complex treatment problem, and cannabinoids have the potential to provide a multidimensional solution to this issue due to the wide range of activities on numerous pain pathways [107]. This is the property that enables cannabinoids to attend to the neural damage combined with the inflammatory factors that frequently occur in these conditions and possibly provide a more holistic approach to the management of pain compared to single-target agents [104]. In the example, cannabinoids have been shown to reduce the chronic secondary headache, orofacial pain, and musculoskeletal pain, all of which often include mixed pain etiologies [103].

Cancer-Related Pain

Nabiximols, which is a cannabinoid-based medicine, has been found to have a lot of potential as an adjunctive analgesic medication in refractory chronic pain, including cancer-related pain, with improvements in pain intensity and a decrease in analgesic use being observed in clinical registries [113]. Such a multimodal response concurs with the multimodal symptom care needed in oncology, which also includes the reduction of symptoms such as nausea, vomiting, and loss of appetite along with managing the pain aspect and hence improves the overall quality of life experienced by cancer patients [114]. Moreover, anti-inflammatory properties of cannabinoids, which are conducted by most of the CB2 receptors, make them useful in the treatment of cancer pains and particularly where the inflammatory mechanisms play a major role [115].

Post-Surgical Chronic Pain

Cannabinoids also can manage chronic post-operative pain by regulating the immune system response and preventing neuroinflammation that can be prolonged following tissue injury and preventing the progression of acute to chronic pain disorders. In addition, their opioid-sparing properties may be especially helpful in the post-operative environment where the use of opioids is likely to result in the emergence of adverse effects and long-term dependence [104]. This also puts cannabinoids as a useful element of multimodal analgesic protocol, which may have a beneficial effect on patient outcomes and diminish the morbidity of opioids used in the post-operative period [116].

Moreover, cannabinoids can be used to treat chronic postsurgical pain which interacts with peripheral cannabinoid receptors and inhibitory pain descending pathways and offers a more extensive analgesic impact compared to conventional monotherapies. With these various mechanisms, cannabinoids are also becoming a multifunctional agent in the treatment of several chronic pain conditions either using cannabinoids as monotherapy, replacement therapy, or even as an adjunct to conventional therapy. The studies that have provided indications of significant pain reduction and high response rate have added more weight to the efficacy of cannabis in chronic pain management [103]. Nevertheless, recent discoveries showed that cannabidiol oil failed to reduce opioid use in cancer patients despite showing promising results in certain groups, which leads to the necessity to acquire a more subtle insight into the effectiveness of cannabinoids in various etiologies of pain and groups of patients [117].

A Comparative Safety and Tolerability Profiles Analysis

The section is a systematic assessment of the adverse effect profile and safety of both opioid and non-opioid pharmacological interventions such as cannabinoids as a chronic pain treatment. These profiles are important to understand comprehensively to inform clinical decision-making and maximize patient outcomes because each of the classes of pharmacotherapy has unique risks. A variety of severe side effects, such as opioid-induced hyperalgesia, endocrine dysfunction, and gastrointestinal complications, among others, are also linked to the long-term opioid use, as well as the previously well-documented health side effects of dependence and addiction [37]. Non-opioid pharmacological interventions, on the other hand, however with a lower risk of dependency, have a range of adverse events, so it is important to consider the comorbidity of the patient and possible drug interactions [104].

This comparative analysis will outline the particular safety issues, contraindications, and monitoring variables of each therapeutic group with the need to consider the imperative to provide risk-benefit evaluations, which are patient-specific. Specifically, even though cannabinoids are a promising alternative due to their interaction with the endocannabinoid system and the ability to alter pain and inflammation, their long-term safety and efficacy, particularly in particular patient groups, including the elderly, or patients with multiple comorbid events, are the areas that require further research [104,118].

Gastrointestinal Effects

To illustrate, the impacts of cannabinoids on the gastrointestinal motility and the possible interactions between cannabinoids and drugs commonly prescribed to treat gastrointestinal conditions should be

considered more thoroughly with the aim of aiding patient safety [119]. Moreover, the cases of nausea and vomiting are a common adverse event among patients treated with oral cannabinoid preparations and should be highlighted as reasons to engage in thorough monitoring of safety [111]. Other typical adverse events triggered by cannabinoid use do not necessitate the increase in severity, except euphoric mood, headaches, and agitation, among which are considered gastrointestinal [120]. However, anxiety, panic attacks and confusion have been reported as psychoactive effects in a small portion of patients, especially when tetrahydrocannabinol rich products are used [112].

Cardiovascular Risks

Although less frequent, cardiovascular effects have been been related with certain cannabinoid preparations including tachycardia and orthostatic hypotension that will require close attention to monitor, particularly in patients with underlying cardiac failure. Also, the psychotropic properties of cannabinoids, such as mood and perception changes, should be adequately instructed to patients and individualized in accordance with dosage regimens to reduce possible neuropsychiatric adverse events [121]. On the other hand, the common use of traditional non-steroidal anti-inflammatory drugs used in chronic pains may cause severe gastrointestinal, renal and cardiovascular problems especially when used persistently and on greater dosages [122].

Furthermore, some anticholinergic medications and N-methyl-D-aspartate receptor blockers, although useful in the treatment of specific pain, may cause various side effects such as thought problems, stomach complications, and neurological problems [123]. Thus, the detailed knowledge of the individual adverse event patterns of each pharmacological group is important in customizing treatment schedules to patient-specific requirements and reduce iatrogenic morbidity. Namely, delta-9-tetrahydrocannabinol has been associated with tachycardia and hypotension with a poorly understood mechanism, which may include anticholinergic action [105].

Renal and Hepatic compromised

Another significant issue is the hepatotoxicity of cannabis-based medicine especially at higher doses of cannabidiol and presents itself as increased liver enzymes [113]. This causes the hepatic functionality to be closely monitored especially in patients who have a pre-existing liver problem or patients who are on concomitant liver-toxic drugs. Nevertheless, research shows that most of the adverse events involving cannabinoids are mild to moderate in nature, and usually remitted by modifying the dose or stopping the drug [111]. Moreover, it should be noted that cannabis-based products should be prescribed with caution to patients with renal or hepatic impairment since metabolism of cannabinoids is mostly located to the liver through cytochrome P450 enzymes and, therefore, may result into altered pharmacokinetics and adverse events [113]. Such a complex metabolic route requires close dose titration and surveillance and especially in groups where hepatic and renal impairment is possible [124]. These considerations hold the greatest importance, given the noted adverse event rates, with 7.7 percent of patients reporting serious adverse events in certain groups, but only a part of them could be linked directly to the study product [125].

Neurological and Psychiatric Effects

The neurological and psychiatric health of cannabinoid use during long-term usage, particularly with a high concentration of THC, has not been fully comprehended yet, with new evidence showing that it may have some adverse impacts [126]. Particularly, cannabis use, especially among adolescents, has been linked to cognitive impairment and a higher likelihood of psychosis and schizophrenia, which are major concerns to the vulnerable groups [117,127]. Additionally, the exact pathophysiology of these neuropsychiatric sequelae, especially in relation to dose-dependent outcomes, and genetic disposition, should be studied more to improve clinical recommendations [128].

These adverse effects are further complicated by the interaction between the cannabinoid profiles and personal neurochemical sensitivities, which makes it difficult to predict and control such outcomes. The

pre-existing psychiatric diseases and substance abuse history must, therefore, be carefully screened before starting the cannabinoid therapy [129]. Moreover, it has been reported that sustained tetrahydrocannabinol exposure, especially in adolescence, might result in heightened pro-inflammatory cytokines in peripheral macrophages, the hippocampus, the hypothalamus, and may be the mechanism by which some of the described neuropsychiatric aspects are mediated [100].

Danger posed by overdose and death

The risk of dying as a result of cannabis overdose is exceptionally minimal, similar to opioids, but the possibility of acute intoxication and impairment, especially of psychomotor abilities and cognitive functions, should be regarded as a serious issue, which is one of the reasons why motor vehicle accidents are among the associated risks [101]. Additionally, using substances in a polypharmacy, in particular, central nervous system depressants, considerably increases the chances of adverse events and death, which underlines the necessity of a thorough examination of the patient [130]. It requires an in-depth analysis of the medication regimen and lifestyle aspects of every patient to determine possible synergistic toxicities and enact the relevant harm reduction measures [101]. However, the safety profile of medical cannabis is not clearly defined in the long term, and some meta-analyses carried out in the chronic non-cancer pain context indicate that the safety of medical cannabis is probable in the course of observation up to 12 months [131]. Such a small observational study highlights the significance of larger longitudinal research to fully describe the long-term safety and effectiveness of cannabinoids in the reduction of chronic pain [132,133].

Long-term Outcomes and Quality of Life

In addition to the immediate analgesic effect of chronic pain management, one of the most important parameters of such management is the evaluation of the effect of therapeutic interventions on the functional status of a patient, psychological well-being, and the quality of life, in the long term. The assessment of these wider outcomes will be a holistic approach beyond plain pain scores, including the measurement of such aspects as activity levels, sleep quality, and mental health. In particular, patients who take medical cannabis often report the improvement of the quality of sleep, which can greatly increase the overall functioning and quality of life, but the definitive, placebo-controlled trials of this effect are still going on [133]. More so, medical cannabis has been anecdotally linked to greater well-being and quality of life, as well as symptomatic management, indicating a larger effect on patient experience [113].

Intensity and Functionality of Pain

Nonetheless, the direct association between the use of medical cannabis and objective gains in functional capacity, including the increase in activity levels or the ability to resume work, needs to be further tightly studied by large-scale and prospective studies. This is especially important considering the fact that there is incongruent evidence as to whether medical cannabis can maintain lasting pain relief without further deterioration of functional limitations, particularly in comparison to traditional therapies. Although certain research has shown that medical cannabis can result in a decrease in opioid dependence and pain outcomes in a few of the patients, the quality of these results is frequently undermined by small sample size and absence of control groups [134] [107]. Nevertheless, there is some empirical evidence indicating that cannabinoid treatment can result in a moderate rise in the well-being of the patient by alleviating the symptoms of mood, appetite, and anxiety, especially in the case of a co-analgesic in cancer-related pain [117].

Clinical Guidelines and Algorithms of treaties

The lack of medical cannabis prescriptive guidelines to use in chronic pain treatment in clinics is a critical challenge to the extensive and adequate implementation of this treatment into therapeutic algorithms, as evidence-based guidelines need to be formulated [133]. Such a gap frequently causes significant differences in clinical practice, which can be largely based on anecdotal reports and personal experience of the clinician, but not on the strong scientific agreement [135]. It is therefore eminent to come up with elaborate guidelines

to deal with proper dosing, route of administration, patient selection, and monitoring guidelines to enhance the best patient outcome and reduce the possible risks. Such guidelines should also outline particular groups of patients who are most likely to respond to medical cannabis such as comorbidities and concomitant drugs to draw definitive signs and contraindications. Moreover, the regulatory agencies should be central in harmonizing the methodologies of research on medical cannabis and make certain that future research will be huge, unbiased, and follow stringent scientific procedures to yield unquestionable results on clinical decision making [136]. This is quite imperative considering that contemporary studies on the use of cannabis-based drugs to treat chronic neuropathic pain still have a lot of uncertainty about the real location of the therapeutic drug [101].

Even in the face of these difficulties, there are certain clinical guidelines to the management of patients who use cannabis as pain medication, which provide preliminary information to guide clinicians and evaluate safety issues and aberrant cannabis-related behaviors [137]. The uneven nature of the various jurisdictions in their regulation of cannabinoids complicates this further since some jurisdictions are allowing the use of cannabinoids in pain management, whereas others are strictly limiting its use even though the pain indications are not formally approved [103]. This regulatory fragmentation helps in creating discrepancies in the accessibility and availability of care and treatment to patients, as well as reinforces inequities in pain management in various geographical areas. Even among the nations, the inconsistency of multiple professional organizations confounds clinicians and patients in the quest to know the role of cannabis-based medicines in chronic pain [101,126].

This uncertainty highlights how essential it is to have a globally concerted evidence-generation method and regulatory authority to assist in bridging the disparities between the need of the patient, scientific knowledge, and clinical practice [138,139]. This kind of harmonized strategy would also be used to have strong and objective research and come up with internationally accepted guidelines on how cannabis-based therapies should be used in the management of chronic pain [101]. It is highly recommended to conduct randomized controlled trials comparing medical cannabis to the already existing standards of care in the future to ensure that its safety and efficacy in enhancing patient outcomes are clear [133]. Additionally, the evidence regarding the effectiveness of cannabis-based medicines and medical cannabis in chronic neuropathic pain is of low quality, and different findings were observed in the systematic review based on the studies involved [101]. This underscores the need to have standardized methodologies and reporting in clinical trials to enable more direct and reliable comparison of the efficacy of the therapies [140].

Conclusion

The management of chronic pain had changed to being dependent on opioids to a multimodal, mechanism-driven, and personalized treatment process. Although opioids would still not be phased out of severe pain management, its negative adverse event profile and potential for abuse motivates the need to seek safer drugs. Non-opioid drugs, including NSAIDs, antidepressants, anticonvulsants, and NMDA receptor antagonists had proven to be of considerable effectiveness in other chronic pain disorders, with better tolerability and opioid-sparing advantages. This review has highlighted that there was no universal pharmacological class that was effective in all kinds of pain. Instead, a combined methodology that took into account the pain mechanism, physiology of the patient and comorbidities gave better results. The integration of pharmacogenomic profiling, real-time monitoring, and digital health tools allowed clinicians to tailor therapy and decrease adverse drug reactions. However, there were still major issues. Restricted access to special pain care, uneven prescription rates, and the constantly growing opioid crisis all pointed to the necessity to implement balance in therapeutic models. The sustainable pain care required education on rational prescribing, rigorous opioid stewardship, as well as the creation of new, non-opioid analgesics.

Conflict of Interest

The authors declare they don’t have any conflict of interest.

Author contributions

Each author wrote a portion of the manuscript, collected data, edited it, created tables, and was given permission to submit it to a journal for publication. The first drafts of the work are written by the first author and the cross-ponding author's supervisor it.

Ethical Approval

Not Applicable

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