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Role of Cannabinoids in Chronic Pain Management: A Pharmacodynamic Perspective

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ABSTRACT

Chronic pain has been shown to be a huge health burden worldwide with just about 20-30 per cent of the adult population being affected, greatly affecting their quality of life, day to day functioning and their mental health. The standard pain relievers involving opioids and non-steroidal anti-inflammatory drugs have their drawbacks to safety, tolerance and effectiveness over vast periods, hence requiring alternative agents. Cannabinoids, especially tetrahydrocannabinol (THC) and cannabidiol (CBD) have been found to offer great potential as therapeutic agents in their multimodal mode of pharmacodynamic action. This review summarises existing results regarding the pharmacodynamics of cannabinoids in pain management, noting that they exert central CB1 receptor-mediated nociceptive transmission blockade as well as peripheral CB2 receptor-mediated anti-inflammatory effects and influence of neurotransmitter systems such as the GABAergic, glutamatergic and opioid systems. There is evidence to show consistent efficacies in neuropathic pain and promising adjunctive effects on cancer pain, and occasional, but emerging areas of usage taking place in nociceptive pain. Nevertheless, obstacles exist with regards to the methodological heterogeneity, the dosage variability, the safety oriented cognitive and cardiovascular adverse effects and the pharmacodynamic variability caused by genetic polymorphism and drug interactions. Future directions in research need to be centred on further mechanistic research, large clinical trials of standardised dosing in larger populations and subtype specific delivery of medicine with pharmacogenetic profiling to study optimisation of medicine delivery to patients. Recognizing the pharmacodynamics of cannabinoids has key implications in the process of evidence-based incorporation of cannabinoids into clinical practice, in the enhancement of chronic pain control methods, and the creation of safe and effective cannabinoid-based pain relievers.

Key Words:

Tetrahydrocannabinol, Cannabidiol, Chronic Pain, Methodological Heterogeneity, Pharmacodynamic

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1. INTRODUCTION

Chronic pain is a worldwide health problem that millions of individuals experience that increases the burden to health care systems decreasing the quality of life[1]. Although pharmacological treatment has

made improvements in the management solutions of pain, conventional pain management is hard as they are ineffective and present negative effects[2]. Phytocannabinoids found in Cannabis sativa plant have become a potential pain management drug, including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The pharmacodynamics of cannabinoids is important to optimize effects of cannabinoids and achieve better clinical effects and reduce risk in treating patients[3]. This review summarizes existing information of cannabinoids, receptor interactions and analgesic mechanisms with a responsible look at the preclinical and clinical studies conducted all over the world.

Table 1: Summary of Key Studies on Cannabinoids in Pain Management

Author(s) & Year	Title	Study Focus	Key Findings	Implications
Sulcova (2019)[4]	Pharmacodynamics of cannabinoids	Cannabinoids pharmacodynamic principles	Explains the mechanism of action involve cannabinoids acting on CB1, CB2 and other receptors in an attempt to work through pain, appetite and cognition	Emphasizes that it is necessary to comprehend receptor interactions in order to utilize therapeutically optimal scales.
Shehata et al. (2022)[5]	Cannabinoids and their role in chronic pain treatment: Current concepts and a comprehensive review	A review of cannabinoids on managing chronic pain.	Reilly, confirms the efficacy of cannabinoids to the neuropathic pain, points out its safety concerns, and response variability	Integration as adjuncts in management of pain, demand additional clinical trials
Poli et al. (2022)[6]	The pharmacogenetics of cannabis in the treatment of chronic pain	Pharmacogenetic effects on the effectiveness of cannabis therapy	Determines genetic polymorphism (e.g. CNR1, CYP enzymes) with regards to efficacy and tolerability	Recommends genetic profiled cannabinoid treatments
Matos et al. (2025)[7]	Cannabis for chronic pain: Mechanistic insights and therapeutic challenges	Procedures and barriers of cannabis based pain treatment	Investigates the endocannabinoid system functions, medicinal possibilities and regulation constraints	Focuses on the mechanistic studies and overcoming the legal/policy issues on the efficient clinical implementation
Halawa, Furnish, & Wallace (2018)[8]	Role of cannabinoids in pain management	Canabinoid in pain medicine clinic	Summarizes clinical competence, modalities, and	Advocates relatively careful evidence-based administration

			combination with the main analgesics	especially in treating neuropathic pain and cancer

1.1. Background

Chronic pain is a highly complicated health issue converting 20-30 percent of adults across the globe and the problem itself affects different conditions such as neuropathic pain, osteoarthritis pain, chronic low back pain and cancer-related pain. It largely affects the normal life activity, physical locomotion, psychological well-being and general living standards[9]. Phytocannabinoids such as THC and CBD and cannabinoids have been considered viable candidates to treat chronic pain. Psychoactive properties of THC are carried out by means of CB1 receptors and the various receptor-based mechanisms of CBD allow it to possess anti-inflammatory, analgesic, and anxiolytic properties. Other relatively less studied cannabinoids such as CBG and CBN are also under study in terms of pharmacological effect. They, therefore, have an important role in pain pathway modulation, which is significant in terms of achieving safer ways of analgesic management in chronic pains.

1.1.1. Chronic pain: Definition, prevalence, impact

Definition

According to Treede et al. (2015), chronic pain can be considered as a pain that takes longer to heal compared to the time of tissue healing which is taken to be three months and may occur despite the lack of continued tissue lesions hence in itself a disease leading to pathology."

As stated by International Association for the Study of Pain (IASP, 2020), chronic pain can be described as pain that continued or recurred beyond a time limit of three months and is no longer seen to be only a symptom, but is a disease in its own right because the disease has complex biological, psychological and social aspects associated to it."

Turk and Okifuji (2001) in the unique definition of chronic pain that was endorsed by the IASP, chronic pain is defined as an unpleasant sensory and emotional experience linked with actual or potential tissue damage, and described in relation to tissue damage, that continues beyond the usual course of healing and resorts in large distress or disability."

According to Merskey and Bogduk (1994) in the IASP Task Force the definition of chronic pain refers to pain which lasts longer than one would normally expect the healing process to continue which is normally three months and it may or may not have a known cause and can thus impair both the physical and emotional status of the patient."

Prevalence

Chronic pain has been identified as being one of the most common health conditions world over with the estimates showing that between 20 to 30 percent of adults in any country are affected by chronic pain[10]. Researchers have determined that there are significant differences in the prevalence rates based upon the population qualities, diagnostic definitions and a variety of research methodology. As an example, around one in five adults living in Europe states to experience moderate to severe chronic pain, whereas, in Australia, the number of people living with chronic pain is approximately 3.4 million people which is an equal of about 17% in the total population. The prevalence of this condition lies in the range of 15 to 25 percent in Asian countries including Japan and China which means that this condition is very prevalent in different healthcare systems, as well as cultural settings[11].

Additionally, epidemiological data also indicate that the prevalence of chronic pain increases with older age with people in their old age being the most affected as a result of degenerative and inflammatory disorders like osteoarthritis, spinal disorders, and neuropathies. Also, gender disparities are also not a secret, where women report higher rates of prevalence and display increased pain intensity and duration in general than men and may be attributed to biological, hormonal, and psychosocial factors[12]. Chronic pain is a common disorder in the United States among adults with an estimate of 50 million adults having chronic pain and nearly 19.6 million having high-impact chronic pain that has impairments related to daily activities and limited engagement. The most frequently reported types of pain are low back pain, osteoarthritis pain, neuropathic pain fibromyalgia, and chronic headache disorders, which individually bring a considerable burden of chronic pain on people and the healthcare systems urged to treat them.

Impact

Chronic pain has an incredibly wide-ranging effect, and the influence of pain is not limited to the physical state of being in pain. It has great effects on the daily activities and physical movement that disable an individual to carry out the normal everyday assignment, occupational activities and the capability of remaining autonomous. Chronic pain causes persistent fatigue, impaired physical fitness, and muscle deconditioning in many patients with chronic pain because they avoid movement and foreign to activity[13]. Moreover, chronic pain is strongly related to psychological distress and may lead to mental disorders, including depression, anxiety, irritability, and mood disorders that in their turn stimulate the perception and severity of pain. Sleep disturbance is also quite frequent, with difficulty getting off to sleep, frequent awakenings and non-restorative sleep all disproportionately exacerbating fatigue and pain sensitivity.

The costs of chronic pain are huge in terms of the economy. This is associated with high direct costs on healthcare as a result of attending medical consultations, diagnostic tests, pharmacological interventions, and interventional therapy[14]. In addition, it causes a large number of indirect expenses through loss of productivity, absenteeism, presenteeism (working but with low productivity due to pain), and long-term disability insurance. On a social level, it is evident that chronic pain is a significant societal health problem, which reduces the efficiency of the workforce, and an issue that causes economic burden to healthcare systems and finances. At the personal level, it compromises individual liberty, social integration and emotional well being with the common outcome of isolation misrelationships, poor quality of life and a feeling of being hopeless and losing purpose. All these aspects of multidimensional effects of chronic pain underline one more time the necessity of effective and integrated approaches to pain management.

1.1.2. Overview of cannabinoids (THC, CBD, others)

Cannabinoids are biochemically active substances in the Cannabis sativa plant, the delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most well known and medically useful cannabinoids[15]. The major psychoactive chemical of the cannabis plant is called THC that is a partial agonist of the CB1 receptors in the central nervous system and CB2 receptors in the immune system and peripheral tissues. It generates analgesic, antiemetic, appetite-enhancing as well as psychoactive effects. CBD instead is a non psychoactive cannabinoid that has a very broad collection of healing effects[16]. It activates the endocannabinoid system indirectly, preventing fatty acid amide hydrolase (FAAH), and exacerbating endocannabinoid ones. CBD also has effects on the non-cannabinoid receptors and ion channels and it adds to the analgesic, anti-inflammatory, anxiolytic, anticonvulsant, and neuroprotective properties of CBD. More than 100 minor cannabinoids have different pharmacological characteristics because of the chemical structure of the cannabis plant. The knowledge of these differences is vital in the maximization of their clinical application and the reduction of the dangers associated with them.

1.2. Objectives of the Review

- To analyze pharmacodynamic mechanisms of cannabinoids in chronic pain management
- To critically assess current evidence on efficacy and safety

1.3. Importance of the Topic

The need to investigate the role of cannabinoids in the treatment of chronic pain relates to the severe constraints connected with common painkillers (opioids and non-steroidal anti-inflammatory drugs (NSAIDs)[17]. Opioids are effective with acute pain, but their tolerance, dependence, and addiction risks, as well as the related risks of respiratory depression (including the life-threatening consequences of the condition), make it one of the major causes of opioid crisis in most countries. The use of NSAIDs on the other hand, causes adverse effects on the gastrointestinal tract, kidneys, and cardiovascular systems especially when they are used in the long run and this becomes a challenge in the case with chronic pain patients. These shortcomings have prompted the repeated demand of alternative or adjunctive pain medications with a documented capacity to provide significant pain relief, and a much more desirable profile when considering a favourable safety risk[18]. In this regard, use of cannabinoid therapeutics has been of growing interest, which has been fuelled by the recent evidence that cannabinoids exhibit analgesic, anti-inflammatory and neuro-modulatory properties and they have the ability to act on pain via new and distinct pharmacodynamic pathways, that are not shared by traditional analgesics. This increased interest helps reinforce the importance of learning how cannabinoids operate in the human body to assist in evidence-based clinical use and better outcomes of pain management within an individual.

2. OVERVIEW OF CANNABINOIDS

Cannabinoids are bioactive substances that are derived out of the Cannabis sativa Plant and may be produced endogenously in the human organism or they may be subjected to laboratory synthesis. They work by interacting with the body cannabinoid receptors with multiple physiological and pharmacological effects. The two phytocannabinoids most investigated include delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The psychoactive component linked with the use of cannabis is termed as THC, where it behaves as a partial agonist in CB1 receptors located in central nervous system. Unlike the other, the CBD is non-psychotic and has a wide therapeutic value. It has complex drug activity, such as the indirect effect on the endocannabinoid system and direct ones on other receptor systems. It holds a bright future in the treatment of most illnesses such as chronic pain, epilepsy, as well as anxiety disorders. There are in excess of 100 minor cannabinoids that are present in the cannabis plant who all possess exclusive pharmacological profiles. Anandamide, 2-arachidonoylglycerol, are among the endogenous neurotransmitters manufactured by the body and binding to cannabinoids rectors in the body to modulate the physiological processes. Synthetic cannabinoids act similarly to phytocannabinoids but usually differently in affinity to the receptors and pharmacokinetic pattern, which has consequences on their effectiveness and safety [19].

2.1. Types of Cannabinoids

The study of cannabinoids has taken three broad categories namely, phytocannabinoids, synthetic cannabinoid and endocannabinoids based on their origin. These various classes have their own special chemical structures and drug actions with varying effects on physiological and therapeutic actions.

- **Phytocannabinoids**

Natural occurring cannabinoids are phytocannabinoids, which are found in the Cannabis sativa plant and are more than 100 in number. THC is the main psychoactive constituent, which has a partial agonist effect at CB 1 to cause euphoric effects whereas CBD, which is not psychoactive, has diverse effects in the therapeutic effects. Other smaller phytocannabinoids are cannabigerol (CBG), cannabinol (CBN)

and cannabichromene (CBC). The compounds are a foundation of numerous therapeutic preparations made of cannabis that possess antibacterial and anti-inflammatory properties, sedative effect, analgesic and anti-inflammatory effects, etc.

- **Synthetic Cannabinoids**

Synthetic cannabinoids refer to drugs which have been designed in the laboratory to resemble the workings and structure of the naturally occurring cannabinoids. Chemotherapeutic nausea and vomiting and stimulating appetite in AIDs-related cachexia are the indications of the medically approved synthetic analogues dronabinol and nabilone. Designer synthetic cannabinoids are made to achieve recreational effects (such as spice or K2) and have an increased psychoactive potency. There is however concern regarding their safety because of possible toxicities.

- **Endocannabinoids**

Endocannabinoids are neurotransmitters, which are lipids, and regulate physiological functions that include two major endocannabinoids namely anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Anandamide controls mood, pain, appetite and memory, the 2-AG controls pain, immune system response and protection of nerves. They are produced upon demand synthesis of precursor membrane phospholipids and they are broken down via enzymes such as FAAH and MAGL. The endocannabinoids system, which is composed of ligands, receptors as well as metabolic enzymes is known to play an important role in establishing homeostasis in pain regulation, immune response, nervous appetite control, and neuroprotection.

2.1.1. Cannabinoid Receptors

The largest contribution to the mechanism of action includes the interaction of cannabinoids with the receptors in the endocannabinoid system CB1 and CB2 receptors and other types of non-cannabinoid receptors, including the TRPV1 and GPR55, to produce the physiological and pharmacological effects. The knowledge of these receptors is central towards the explanation of the pharmacodynamics of cannabinoids during the management of chronic pains [20].

- **CB1 Receptors**

CB1 receptors (Cannabinoid receptor type 1) are G-protein coupled receptors (GPCRs), which are mainly found in the central nervous centre (CNS), the brain among other regions which are involved in inhibition of pain; these areas contain the periaqueductalgray matter, thalamus, basal ganglia, hippocampus and the dorsal horn of the spinal cord. They also occur in peripheral tissues though in lower concentrates: adipocytes, liver and gastrointestinal tract. The CB1 receptor activation by endogenous (anandamide, 2-AG) or exogenous (THC) cannabinoids leads to adenylate cyclyase inhibition, a decrease of cyclic AMP level, ion channels regulation (the center closing of voltage-gated calcium and opening of potassium), and, consequently, neurotransmitter release inhibition. The result is less excitability in neurons and analgesics. The psychoactive and cognitive effect of THC (i.e., euphoria, altered perception, and poor memory) may also be due to the activation of CB1 and may restrict its use as therapeutic medication.

- **CB2 Receptors**

CB2 expression is mainly believed to be present in peripheral tissue especially in the immune system with expression in the spleen, tonsils, thymus, immune lymphocytes (B and T lymphocytes and macrophages and microglial cells in the central nervous system (CNS). CB2 Receptors are of the GPCR type and on activation, contribute to the migration of immune cells, production of cytokines, and affects inflammation. In contrary to CB 1 receptors, CB 2 receptor activation is not psychoactive and, therefore, the receptor offers an interesting therapeutic opportunity in the treatment of inflammatory and

neuropathic pain. Recent research has shown the CB2 receptors have been upregulated in the pathological pain states and when they are stimulated by an agonist they stimulate analgesic and anti-inflammatory effects by causing a decrease in the peripheral and central sensitivities, neuroinflammation, and tissue damage caused by immune-medication.

- **Other Receptor Targets (TRPV1, GPR55, etc.)**

In addition to CB1 and CB2 receptor constituents, supplementary pharmacodynamic properties of cannabinoids are through non-cannabinoid receptors and interactive ion channels[21:]

- **TRPV1 (Transient Receptor Potential Vanilloid type 1)**: TRPV1 and/or capsaicin receptor, is a non-selective cation-selective channel that deals with pain sensation and neurogenic inflammation. CBD and anandamide have the potential of activating TRPV1 receptors resulting in desensitization of the nociceptive pathways and would have some analgesic effects especially in neuropathic and inflammatory pains.
- **GPR55 (G-protein coupled receptor 55)**: Also called the third cannabinoid receptor, the GPR55 is highly present in the brain, bone, and immune cells. GPR55 GPR55 activation by specific cannabinoids activates the calcium signal pathway and this explains its effects on pain perception, inflammation, and bone physiology. Nonetheless, its precise in the context of cannabinoid pharmacology is an actively studied area of preparation.
- **PPARs (Peroxisome proliferator-activated receptors)**: Stimulation of nuclear receptors by cannabinoids like CBD may include PPAR-g, inflammation, lipid metabolism regulation, and insulin sensitivities. The neuroprotective and anti -inflammatory response to cannabinoids is mediated by the activation of PPAR-g.
- **5-HT1A receptors (Serotonin receptors)**: CBD was demonstrated to be an agonist of 5-HT1 A receptors, and it has anxiolytic and analgesic effects through the modulation of neurotransmission of serotonin.
- **Glycine receptors and opioid receptors**: Some cannabinoids interact with glycine receptors in the spinal cord and promote their inhibitory neurotransmission, whereas synergistic effects with opioid receptors are another factor to their analgesic effect.

2.2. Pharmacodynamics of Cannabinoids in Pain Management

The pharmacodynamics aspect of the cannabinoids is vital in comprehending the analgesic effects of the cannabinoids in the process of pain management. These agents have affinity to multiple pain receptor, ion channels, and signaling pathways to regulate pain perception and response. They operate by a multimodal system and affect central and peripheral nociceptive processing, Neuronal excitability, and neurotransmitter release[22]. They have an analgesic, anti-inflammatory, and neuromodulatory effect by binding receptors both cannabinoid and non-cannabinoid and inhibit the release of neurotransmitter, decrease inflammatory responsiveness, and restrain the signal pathway of pain. Pharmacodynamics of cannabinoids is the key to maximizing therapeutic properties of clinical application, maximizing therapeutic advantage, and creation of novel analgesics.

2.2.1. Mechanisms of Analgesia

The analgesic effect of cannabinoids can be accomplished by both variance and peripheral destinations which permits them to habitually manipulate the sensation of agony at the various levels of the nerve system. Such multimodal behavior helps them to cope effectively with different forms of chronic pains.

- **Central Mechanisms**

The major mechanism that cannabinoids act as a central analgesic is through modulation of the CB1 receptor in the central nervous system. Those receptors prevent stimulate neuroparticular movements of the neurotransmitters and lower the excitability of the nerve cells and suppresses pain transmission. They regulate also the downward inhibitors of the pain pathways by amplifying the release of inhibitor neurotransmitters such as GABA and serotonin. Central mechanisms deal with interactions with other receptor systems, e.g. TRPV1 and opioid receptors with synergistic analgesic effects. Nevertheless, the psychoactive effects may be attained by the activation of the CB1 receptors thereby perhaps restricting the medicinal purpose of some cannabinoids such as THC.

- **Peripheral Mechanisms**

Cannabinoids recruit peripheral analgesia via predominant CB2, which is located in immune cells, peripheral nerve terminals and inflammatory locations. The stimulation of the CB2 receptors leads to the blockade of the pro-inflammatory cytokine release, inhibition of the movement of the immune cells, as well as the decreasing of the local inflammation, which means the reduction of the peripheral sensitization and the activation of the nociceptors. Also, cannabinoids can regulate the functioning of the peripheral sensation neurons by stimulating the TRPV1s and thereby desensitizing the nociceptors and compromising the transmission of distressing feeling to the central nerve system. Having focused on peripheral mechanisms, cannabinoids can give pain relief without the central psychoactivity of CB1 receptor activation, and are potentially of interest as therapeutic agents, especially in inflammatory and neuropathic pain, where peripheral mechanisms of sensitization are paramount.

2.3. Key Research Studies on Cannabinoids and Chronic Pain

Recent trend of research in the use of cannabinoids in chronic pain management has grown because of the need to have safer options. Their therapeutic potential, pharmacodynamics, and restrictions can be learned following the preclinical experiments and clinical evaluations and help emphasize future investigations in the cannabinoid-based pain management[23].

2.3.1. Preclinical Studies

In the preclinical studies, animal models have been employed to learn the effectiveness and mechanism of cannabinoids in pain management. Such studies are painful since they replicate different forms of pain, such as inflammatory, neuropathic, and cancerous-related pain. According to animal research, cannabinoids such as those found in THC, CBD, and synthetics cannabinoid agonists alleviate pain behaviors[24]. The use of CB1 receptors in the central nervous system prevents neurotransmission of nociceptive transmission, whereas CB2 receptors in peripheral tissue and immune cells reduce inflammatory reactions. Cannabinoid-induced analgesia occurs through non cannibinoid receptor such as TRPV1 channels. Enhanced analgesic effects of synergy could result in opioid doses lower than those of cannabinoids alone and achieve reduced side effects. But metabolism, dosage and distribution of receptors between animals and man means that a careful interpretation is needed and that clinical studies have to be performed.

2.3.2. Clinical Studies

There have been clinical investigations on the potential of cannabinoids therapy in the management of chronic pain in terms of randomized controlled trials (RCTs) and observational studies. These stringent approaches examine the effectiveness and safety of THC, CBD alone or in combination in dystonia, arthritis and musculoskeletal pain.

- **Randomized Controlled Trials (RCTs)**

Randomized controlled trials (RCTs) are regarded as the gold standard in the clinical research investigation, as they give high-quality evidence concerning the effectiveness and harmlessness of an

intervention, as they reduce the risk of bias[25]. Regarding chronically experienced pain, various studies have used RCTs to study the effectiveness of THC, CBD, and their mixtures in different types of pain, such as neuropathic pain, cancer pain, fibromyalgia, musculoskeletal pain. These studies have shown that cannabinoids have the potential to cause marked decreases in pain levels, better sleeping schedules, and an increase in patient-reported outcomes as opposed to a placebo. An example is the studies of nabiximols (a spray containing THC:CBD in an oromucosal form) which have indicated positive results in cancer pain that is resistant to opioids and nabiximols have also demonstrated positive improvements in neuropathic pain related to multiple sclerosis. Nevertheless, RCTs have also been used to identify limitations, including variability in individual responses, psychoactive side effects when using THC-dominant preparations and difficulty in defining optimal dosing regimens because of differences in pharmacokinetics and preparations. On the whole, RCTs present evidence of the effectiveness of cannabinoids as adjunctive analgesics, with results pointing to the significance of personalized treatment strategies and the necessity of additional large-scale trials to establish long-term outcomes of the medication and its efficacy.

- **Observational Studies**

Observational studies would provide a complementary method of assessing the effectiveness and safety of cannabinoids in different patients populations and over a protracted period that the RCTs could not. These come in form of cohort studies, case series and cross-sectional surveys, which were all of value in terms of patient-reported benefits, side effects, use patterns, and quality-of-life enhancements. As a case in point, observational studies have described an observation in patients with chronic pain who use medical cannabis, which is the occurrence of a lower degree of pain, lesser usage of opioids, enhanced sleep, and superior functional outcomes. In addition, studies raise such practical issues as inconsistency of strains or doses of cannabis and methods of administration by patients in usual care. Observational studies have weaknesses of confounding factors and lack of randomization, despite that, provide a great deal of knowledge about the acceptability, tolerability and actual effect of cannabinoid-based therapies, which can be applied to clinical recommendations and even policymaking.

3. METHODOLOGIES IN CANNABINOID RESEARCH

Cannabinoid studies involve different methods and strategies of experimentation and clinical trials to assess pharmacological effects, efficacy, safety, and therapeutic potential of cannabinoids in the management of pain. The preclinical methods involve in vitro experiments and animals and clinical studies employ randomized trials and observational studies. Sophisticated methodologies employ neuroimaging to know how cannabinoids influence activities of the brain and pain management. Scientific evidence on the efficacy and safety of cannabinoids is borne through systematic review and meta-analyses.

3.1. Experimental Designs

Experimenting designs in the study of cannabinoid researches involve an assessment of the effect using pharmacodynamic tests and a scale of pain in measuring the effectiveness in the management of chronic pain. The kinds of tests used are to show how cannabinoids will interact with the receptor targets besides the fact that pain assessment scales are used to show how much the pain is, the quality and the effectiveness of treatment used on it.

Pharmacodynamic Assays

Pharmacodynamic assays are necessary experimental methods adopted in the cannabinoid studies to determine the biochemical and physiological responses of cannabinoids on cellular and systemic activities. Such assays also measure receptor binding studies because they evaluate the selectivity and affinity of cannabinoids to CB 1, CB 2 and other receptor targets like TRPV1 and GPR55 to understand

how they act. Assays which quantify the downstream signalling events which occur following receptor binding and therefore determine the potency and efficacy of cannabinoids to act as agonists, partial agonists or antagonists include functional assays e.g. G-protein activation assays and cAMP inhibition assays. Also, anti-inflammation, neuroprotective, and analgesic effects of cannabinoids are evaluated in cultured neurons or immune cells, in vitro, measuring the variations of cytokine/ion channel/neurotransmitter. The conduct of these pharmacodynamic assays has served as the foundation of cannabinoid mechanism of therapeutic action and served to inform the dose selection and formulation development of studies conducted in humans[26].

Pain Assessment Scales Used

Pain measurement is an important part in experimental and clinical cannabinoid studies to establish the efficacy level of pain. Throughout animal models, behavioural approaches that determine the nociceptive threshold, pain tolerance, and inflammatory pain intensity are demonstrated; these approaches include the tail-flick test, hot plate test, von Frey filament examination, and the formalin test, among others, used to quantify the effects of cannabinoids. During the clinical trials, different and used validated pain assessment scales are used in order to obtain the patient report outcomes. These are Visual Analogue Scale (VAS) in which patients scale pain on a continuous scale, Numerical Rating Scale (NRS) scale in which the scale uses numbers to rate the level of pain, and McGill Pain Questionnaire (MPQ) which measures the sensory, affective and evaluative aspects of pain. Other scales like Brief Pain Inventory (BPI) measure pain level and how the pain affects the daily life and functioning in life. The scale used in pain assessment is based on the type of study, patient population, and the pain condition under study are the key factors in the reliable and replicable assessment of the cannabinoid analgesic effects.

3.1.1. Strengths and Limitations

Randomized, controlled trials, preclinical investigations, and observational information are some of the strength requirements on research about the use of cannabinoid in managing chronic pains. Nonetheless, the forms of bias in the study design, small sample sizes, variation in formulations, dose, and routes of administration, and relative difficulty of blinding because of the psychoactive effects of THC are the barriers.

Strengths

The studies which concern cannabinoids in chronic pain management have a number of strong points. Randomized controlled trials (RCTs) are methodologically aligned with the utilization of the randomization of possible reflective variables, the blinding of the observations requirements, the use of a placebo, to reduce the confounding variables and offering high-quality evidence concerning efficacy and safety. The preclinical research provides the mechanism of action of cannabinoid pharmacodynamics and pharmacokinetics, the interaction of cannabinoid receptors and the mechanism of analgesia, which contributes to the solid basis of clinical translation. There is also an addition of observational studies that provide the real-life evidence regarding the effectiveness in the long run, preferences that may be given by the patient and also the tolerance among the population. Application of validated scales to measure the pain guarantees consistency in the measurement of the outcome, which makes the results more comparable between the studies. In addition, the pharmacokinetic and pharmacodynamic investigations enhance the challenge of the absorption, metabolism processes, and receptor binding of cannabinoid to make the determination of optimal dosing approaches.

1. **Small Sample Sizes**: Small sample sizes common in many studies, including clinical trials, make the applicability of results difficult and decrease statistical power to identify important differences not only overall but also in subgroup analysis of pain type, sex, or comorbidities.

2. **Biases in Study Design**: There exist the following types of bias: selection bias via the berustation of strict eligibility criteria, the performance bias by the studies that are not blinded sufficiently, and the reporting bias by selective reporting of positive results that influence the validity of conclusions.

3. **Dosage Variations and Heterogeneity**: Across the studies, heterogeneity is high, owing to differences in cannabinoid formulations and THC:CBD ratios, routes of administration (including oral, oromucosal and inhalation), level of dosing, which makes it difficult to compare studies and formulate standardized treatment protocols.

4. **Psychoactive Effects and Blinding Challenges**: The psychoactive potencies of THC are problematic to maximize good blinding during clinical trials and have the potential to affect the patient-reported outcomes, which include potential bias in measurements.

3.2. Thematic Synthesis

The thematic synthesis describes how effective cannabinoids are in the management of neuropathic pains, nociceptive pains, and cancer pains. There is also safety, adverse effects, and pharmacodynamic variability that has been discussed since cannabinoid-based pain management requires personalized methods.

3.2.1. Efficacy Across Pain Types

The effectiveness of cannabinoids in different pain types is divergent and they are highly effective in neuropathic pain and improving quality of life. Nonetheless, there is not much evidence in nociceptive pain and not so much consistency in primary therapy. It is important to tailor use according to the mechanisms of pain and the needs of patients[27].

- **Neuropathic Pain**

Neuropathic pain, which is generated either by damage or malfunction of a nervous system, is often hard to treat using standard analgesics. Cannabinoids, especially THC, CBD, and their combinations, have been proven to have average effect in minimizing the neuropathic pain symptoms in clinical research. The pain, sleep and quality of life improved significantly in patients with neuropathic pain due to multiple sclerosis, spinal cord injury, and peripheral neuropathies in randomized controlled trials using nabiximols (THC:CBD oromucosal spray). The analgesic properties of Cannabinoids are mainly explained by the central inhibitory action on the nociceptive transmission by activating the CB1 receptor and modulation of neuroinflammation by activation of the CB2 receptor. Nevertheless, variation in the subjective reactions and the psychoactive adverse effects still pose a questionable situation in the use of cannabinoids in managing neuropathic pain.

- **Nociceptive Pain**

Nociceptive pain is caused by a damaged or inflamed tissue and is generally treated using NSAIDs and opioids. The effectiveness of the cannabinoids use in nociceptive pain is not that well-documented at the level of neuropathic one. Cannabinoids have been reported by some research to offer mild to moderate pain relief in disorders like osteoarthritis and musculoskeletal pains, mostly due to their anti-inflammatory properties that occur during receptor activation of CB2 and TRPV1 desensitization. Evidence is however, weak and inconclusive with few trials showing major superiority to placebo. As a result, cannabinoids cannot be classified as the first-line treatment of nociceptive pain; instead, they could serve as adjunctive therapy, especially in patients who do not respond to conventional drugs.

- **Cancer Pain**

Cancer pain is typically mult factorial i.e. it has nociceptive as well as neuropathic elements to it and it may be resistant to opioids alone. Cannabinoids have been studied in the management of cancer pain, with cannabinoid agents likely to produce improvements in poorly responsive patients (opioid-refractory patients). Nabiximols and THC-dominant preparations have demonstrated efficacy and safety in reducing the pain intensity and improving sleep and overall symptoms control during clinical trials used as add-ons to opioid therapies. There is also a possibility of cannabinoids lowering opioid needs, alleviating opioid associated side effects. Nevertheless, not every study made serious improvements, and the issue in psychoactive effect, sedation, and the acceptance by the authorities in Oncological causes are still of concern. Future clinical trials in a larger segment of the population should define the optimal dosing, efficacy and safety of this drug.

3.2.2. Safety and Adverse Effects

Cannabinoids are dangerous as well as harmful particularly to the central nervous system and to the cardiovascular system. The effects on CNS include cognitive effects and psychotropic effects, whereas the cardiovascular effects include tachycardia and heart disorders. Dose, monitoring, and education of the patient is essential.

- **CNS Effects (Cognitive, Psychotropic)**

Cannabinoids, especially THC content, is linked to effective central nervous system (CNS) responses because of their effects on the CB1 receptors located in the brain. Narcotic effects are common psychotropic events that affect the sense of euphoria, losing the sense of time, sedated states, and poor coordination all of which may result in reducing daily activities and that acquires risks, like motor accidents. It has cognitive effects such as impaired short-term memory, decreased attention span and impairment of executive function, particularly at large doses of THC. Chronic exposure has the potential to increase the dependency, tolerance, and withdrawal symptoms in children (e.g. adolescents) and those who are susceptible to psychological illnesses. Anxiety, paranoia and psychotic-like symptoms have also been reported in some studies especially using high-THC formulations demonstrating the importance of clinical use in dose-titrating and monitoring patients using cannabinoids.

- **Cardiovascular and Other Systemic Effects**

Cannabinoids have several cardiovascular actions; they cause tachycardia, orthostatic hypotension, and dysregulation in blood pressure, and these actions are exerted via the vasodilatory properties and regulating the activity of autonomic nervous systems. The effects are mostly slight, however in other patients with pre-existing cardiovascular disorders like arrhythmias, coronary artery disease or low blood pressure, it can be dangerous. Other reported systemic effects are dry mouth (xerostomia), increased appetite, dizziness and fatigue. Serious adverse events have been described in rare cases including myocardial infarction or stroke in which case causality is not established. Also, cannabinoids when inhaled can produce irritations to the airways or bronchitis type of symptoms, and when taken orally, it is likely to be linked to gastroinstestinal symptoms such as nausea or diarrhoea, especially at high CBD doses.

3.2.3. Pharmacodynamic Variability

Genetic polymorphism and drug interactions contribute to the pharmacodynamic variability in the cannabinoid therapy. Such differences change the sensitivity of the receptors, metabolism, and treatment response which changes efficacy and adverse effect. Knowledge of the pharmacodynamic variability is important in order to optimize dose, reduce risks and individualize therapy in the management of pain.

Influence of Genetic Polymorphisms

Genetic polymorphisms in cannabinoid receptors and metabolic enzymes play a very important role in the pharmacodynamic variability in cannabinoid response. Mutations in the CNR1 gene, which codes the CB1 receptor and CNR2 gene, which codes the CB2 receptor, can cause changes in receptors abundance, affinity, and effectiveness signalling, causing inter-individual receptor variations to change the level of stimulation by cannabis-derived products by steering different people to produce different levels of analgesia, psychoactivity, relatively low information on efficaciousness and tolerability. To give an example, certain single nucleotide polymorphisms (SNPs) in CNR1 could be linked with variations in pain sensitivity and sensitivity to formulations that contain THC. Moreover, gene polymorphisms of metabolic enzymes, including CYP2C9, CYP3A4 and CYP2C19 — which assimilate THC and CBD respectively, respectively, may influence the plasma level, length of the effect, and possibility of the side effect. The existence of these genetic variations underlines the possibility of a personalised cannabinoid treatment, in which pharmacogenetic profiling is used to optimise drug choice and dosing in an individualised context [28].

Interaction with Other Drugs

Interactions between cannabinoids and other medications can occur in a dose-related manner to induce pharmacodynamic and pharmacokinetic interactions that affect therapeutic effectiveness and safety. CBD and THC have been found to have inhibitory or inducing effect on the cytochrome P450 enzymes (CYP2C9, CYP3A4, CYP2C19) increasing or decreasing the metabolism of co-administered drugs like warfarin, opioids, benzodiazepines, antidepressants, and anticonvulsants. This may either lead to higher or lower levels of these drugs in the plasma which may culminate into an elevated pharmacological effect or toxicity. At the pharmacodynamic level, cannabinoids can demonstrate additive or synergistic interaction with the CNS depressant (e.g., opioids, benzodiazepines, alcohol), adding to the danger of sedation, impaired consciousness, and respiratory depression. On the other hand, there may also be an interaction of a stimulant or serotonergic substance hence causing negative neuropsychiatric problems, such as anxiety or agitation. Thus, attention should also be paid to detailed medication reconciliation, signs of drug interactions, and dose optimization in case cannabinoids will be used as one of the components of a multimodal pain management plan.

4. DISCUSSION

It speaks of pharmacodynamic actions of cannabinoids, analgesia in the central and periphery of the human body, and how it can relieve pain. It presents such limitations as inconsistencies in setting methods and insufficient safety gap. Adavanced pharmacodynamic experiments and personalized medicine strategies in the application of the treatment should be considered in future studies as to be applied safely in the clinics[29].

4.1. Interpretation of Findings

- It combines preclinical and clinical evidence studies to determine the mechanism of analgesic effects of cannabinoids in management of chronic pain.
- It points out to there central receptors based inhibition of nociceptive transmission with CB 1 receptors, peripheral CB 2 receptors based anti-inflammatory responses, and neurotransmitter system modulation cultures, as GABAdergic, glutamatergic, and opioid pathways.
- It describes efficacy patterns, with consistent efficacy in neuropathic pain and limited efficacy in nociceptive pain, and possible adjunct effectiveness in cancer pain, with patterns of mechanisms linked to clinical effects to generate a coherent body of evidence.

4.2. Clinical and Research Implications

- Cannabinoids could be used as an add-on or alternative therapy in pain management especially in patients who are not effectively treated by regular analgesic regimes.

- They can fit into multidisciplinary pain management models, as they have multimodal modes of action and can decrease the opioid needs.
- The clinicians should take into account the criteria used in patient selection in other words they should prescribe cannabinoids to the right individuals depending on the type of pain, comorbidities and history of treatment.
- The practical factors to consider encompass performing risk benefit level analysis, identifying proper dosing techniques, observing adverse effects as well as competently handling drug interplays.
- Education of patients on the psychoactive effects, laws and personal responsibilities is necessary, as a strategy to promote safety and optimise therapeutic effects in clinical practice.

4.3. Limitations and Gaps in Current Research

The evidence on long-term safety is still lacking robust data on chronic cannabinoid use, especially in terms of cognitive, cardiovascular and psychiatric effects. Also, no comprehensive research of the effectiveness of dosing strategies, the role of genetic factors in response, drug combination with other pain management systems, and comfort provision has been performed to facilitate the use of research findings confidently in a clinical setting, which necessitates the development of additional specific studies. Together with these gaps in the researches is the identification of number of limitations to the existing researches as highlighted below.

- A lot of research lacks statistical power and is non-generalisable due to their small sample size.
- It has methodological inconsistency with heterogeneity across study designs, cannabinoid formulations, dosing regimens and outcome measures.
- There is a chance of studies being biased i.e., selection bias, performance bias owing to improper blinding, and reporting bias that favours the positive results.
- Dosage and formulation difference between studies make it hard to compare and standardise treatment protocols.
- Hurdles of blinding are witnessed because of the psychoactive nature of THC, which creates a possibility of affecting the patient-reported outcomes.

4.4. Future Research Directions

Priority in the future studies on cannabinoids in management of chronic pain research should centre on carrying further pharmacodynamic research aimed at explaining more detailed actions, and receptor and conjunct pathways in exerting the analgesic effects. These studies would help in the generation of new cannabinoid based pain killers that would have a higher efficacy and fewer side effects[30]. Also, well-designed clinical trials involving large numbers of patients are required so that standardised formulations, dosing regimens and long-term follow-up are established in order to determine definite profile of effectiveness and safety in all forms of pain. The personalised medicine strategies, such as pharmacogenetic profiling of individual responses to cannabinoids on the basis of genetic polymorphism in receptor activity and metabolism, to treat individuals with individualised treatment strategies, should be pursued in research as well. Moreover, research on drug-drug interactions, the most effective ways of incorporating the pharmaceutical with current pain management protocols, and practical experience in different patient groups is important to further reinforce evidence-based clinical prescription and make the best use of pain remedies with limited risk to the patient.

5. CONCLUSION

In conclusion, studies have shown that cannabinoids like THC and CBD have great therapy potential in the management of chronic pains given that they work through multimodal pharmacodynamic

pathways, like analgesia, blocking of peripheral CB2 receptor-mediated anti-inflammatory effects, and neurotransmitter systems. Although there are findings that demonstrate their effectiveness, especially in neuropathic pain and cancer related pain as adjunctive therapies, the setbacks including inconsistencies in conducting the study, inconsistencies in the way different people react to a particular treatment, safety implications, and unavailability of long term data limit the probability of their across-the-board clinical use. This review highlights the significance of more research in highly advanced pharmacodynamics, standardised clinical trials in large numbers, and individualized medicine modalities to streamline the use of cannabinoids. Inclusion of cannabinoids in pain management procedures must also be implemented with proper patient selection, dose optimisation, adverse effect monitoring, and extensive patient education so as to optimise benefits and reduce risks, leading to the more effective and safer control regarding painful conditions on chronic management routes.

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