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Review

# Chronic pain and cannabinoids. Great expectations or a christmas carol

D. Pascual, E.M. Sánchez-Robles, M.M. García, C Goicoechea*

*Farmacología y Nutrición, Facultad de Ciencias de la Salud, Universidad Rey Juan Carlos, Spain*
*Grupo de Excelencia investigadora URJC-Banco de Santander-Grupo Multidisciplinar de Investigación y Tratamiento del Dolor (i+Dol), Spain*
*Unidad Asociada CSIC-IQM, Alcorcón, Spain*

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ABSTRACT

The discovery of the endocannabinoid system nearly three decades ago generated great interest among pain scientists. Moreover, its analogy with the opioid system in terms of evolutionary preservation, tissue localization and analgesic activity enabled a vast new field for the development of medicines addressed to those types of pain that still nowadays are difficult to manage. However, the main disadvantage that hampers the use of cannabinergic drugs as analgesics is their identification with recreational use, besides their psychotomimetic actions. Pain has traditionally been classified attending to the ailment duration (acute or chronic) and drugs are used according to the intensity of the pain to treat, but it is also important to target the mechanism involved despite the intensity or duration of pain. The present chapter reviews the study and use of cannabinoids attending separately to four classic types of pain: nociceptive, inflammatory, neuropathic and oncological, considering basic research (pain animal models) as well as clinical practice.

## 1. Introduction

Pain classifications are useful strategies for a better comprehension of disorders sharing similar durations (acute or chronic) or a common origin (nociceptive, inflammatory or neuropathic). However, different categories may activate overlapping yet distinct mechanisms in pain transmission, displaying a dual component –nociceptive and neuropathic.

On the one hand, nociceptive pain corresponds to a commonly easier-to-treat short- lasting acute pain. However, it may shift into a rather outlasting subchronic pain due to peripheral [1] and/or central [2–4] sensitisation.

Neuropathic pain, on the contrary, originates from direct damage to the nervous system (peripheral or central) by either external (trauma or infections) or internal (vascular, immune or metabolic disorders) sources, which may cause neuroinflammation at either local or distant sites of the injury [5]. Persistent nociceptive inputs is now known to induce plastic changes mediated by activation of both spinal microglia and astrocytes which release pro-inflammatory cytokines perpetuating neuron excitation and therefore the pain condition [6]. Such vicious circle makes neuropathic pain extremely difficult to treat. Since spinal glial activation seems to be the limiting factor for the achievement of long-lasting chronic pain, targeting the signalling pathways responsible for glial activation may break the loop and impaired chronification. Moreover, activation of the immune system seems to have a crucial role in both peripheral and central abnormal sensory processing, and chronic neuropathic pain may now be considered a neuro-immune disorder [7,8]. Microglia are thought to initiate the neuropathic pain processes by the release of proinflammatory chemokines and cytokines that in turn activate astrocytes and leads to further microglia activation [9]. In the neuropathic pain processes, microglia activation decreases to baseline after three weeks, though astrocytes activation and hypersensitivity remains [10,11].

Last, but not least, oncologic pain is probably the most difficult to categorise for being so diverse and varied in perception and mechanistically: irruptive, referred, neuropathic, visceral, diffuse, localised, etc.

Interestingly, the discovery of specific cannabinoid receptors (CB-R) not only on neurons but also on immune cells or cells alike, such as glia, together with the identification of a series of endogenous ligands targeting such receptors and enzymes for the biosynthesis and degradation of such ligands, led to the characterisation of a neuromodulatory endocannabinoid system in mammals [12–15]. Similar to opioid, evidence for a functional endogenous cannabinoid system has been obtained practically for all organisms with a neural network [16,17]. Differential tissue expression of these CB-R but colocalization with opioid receptors

* Corresponding author at: Pharmacology Unit, Basic Health Sciences Department Health Sciences School, Universidad Rey Juan Carlos, Avd Atenas S/N, E-28922 Alcorcón, Spain.
*E-mail address:* carlos.goicoechea@urjc.es (C. Goicoechea).

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advocates for a dichotomic view of the endogenous cannabinoid system on pain management: CB-1 and CB-2 mediated analgesia. CB1 receptors are enriched in the CNS –in fact they are one of the most (if not the most) abundant G-protein coupled receptors (GPCR) in the mammalian brain [18,19]– and constitute the central receptor for psychotropic cannabinoids. They are also present in some peripheral tissues. On the contrary, CB2 receptors are either absent or expressed in low levels by neural tissues but are mainly present on glia and cells of the immune system, although not exclusively, and hence lack psychotropic side effects. Additionally, they are overexpressed in some tissues under inflammatory conditions [20]. The use of animal models has enabled uncovering the mechanisms by which endocannabinoids modulate nerve cell excitability and therefore pain transmission. Nowadays it is generally accepted that endocannabinoids act preferentially in a retrograde manner at a synapse; that is, they are generated postsynaptically but act on receptors in the presynaptic membrane to hinder excitatory neurotransmitter release [21,22]. However, endocannabinoids can also target glial cells diminishing the influence these cells exert on neuronal excitability at the tripartite synapse, but also at glia-neuron or neuron-immunocyte interactions along the peripheral and central nervous system [23,24].

CB receptors activation could also be related to the mechanism of action of other analgesic systems, o drugs, such as opioids or even acetaminophen. Recently acetaminophen has been proposed to act through CB receptors to induce analgesia. In their work, Klinger-Gratz and his collegues, support the involvement of the endocannabinoid system in the analgesic action of acetaminophen against inflammatory pain and identify the RVM and descending antinociceptive fiber tracts as a likely site and mechanism of action [25].

The cannabinoid system has postulated as one of the endogenous systems that modulate pain perception. Three drugs that activate cannabinoid receptors are currently available as commercialised products: Cesamet (nabilone), Marinol (Δ-9-tetrahydrocannabinol + dronabinol) and Sativex (Δ-9-tetrahydrocannabinol + cannabidiol). All of them indicated as analgesic treatment in cancer pain and/or management of neuropathic pain and spasticity associated to multiple sclerosis. Besides, increasing evidence, both from animal and human studies, postulate their utility in other pain conditions. However, the use of cannabinoid agonists, both synthetic and plant-related, is not free from side effects, both in acute and chronic administration, which should be carefully considered. Of particular concern is the possible presence of Cannabis-related psychosis. For this reason, Pharmaceuticals like Sativex should be contraindicated in patients with a previous history of psychosis (or even in patients with a family history of psychosis) [26].

## 2. Nociceptive and inflammatory pain

The analgesic effect of cannabinoids has been known for several decades. For centuries the preparations of the Cannabis sativa plant have been used as analgesics, but until the 1960s the main active constituent (Δ9-tetrahydrocannabinol) was not identified [27]. It was not until the 1990s when CB1 and CB2 cannabinoid receptors were discovered [12,15] and mechanisms and sites of action explained [28–33]. In the last two decades, numerous tools have been developed to modify the endocannabinoid (EC) system, and a large amount of research has demonstrated the potential efficacy of this approach for pain relief [34,35].

The components of the EC system comprise the cannabinoid receptors coupled to the G protein CB1 and CB2, their endogenous ligands anandamide (AEA) and 2-arachidonyl glycerol (2-AG), and their enzymatic systems of synthesis and degradation. These components are expressed ubiquitously along the nociceptive pathways. Endocannabinoids are generated on demand in response to high levels of activity and produce short-term antinociceptive effects, mainly through their binding to CB1 receptors located in nociceptive neurons. Using exogenous cannabinoid ligands or enhancing endogenous signaling, nociceptive transmission can be modulated at multiple sites: in the periphery [36], the dorsal horn of the spinal cord [37–41] and in regions of the supraspinal brain associated with pain.

### 2.1. Data from animal studies

Several pharmacological approaches have been developed in order to activate EC system as an analgesic strategy, focusing to enzyme modulation or receptor activation.

#### 2.1.1. Enzyme modulation

It is known that endocannabinoid levels rise specifically in injury sites [34]. For this reason, many researchers have focused on the use of specific enzyme inhibitors to increase the effects of ECs and thus increase endogenous analgesia without the undesirable systemic side effects associated to exogenous ligands. Fatty-acid amide hydrolase (FAAH) was identified as the major enzyme degrading fatty-acid amides which bind to cannabinoid receptors, such as AEA. This discovery led to the development of several classes of compounds capable of inhibiting FAAH and thus promoting signalling of AEA. These compounds show high specificity for FAAH, significantly elevating levels of AEA, in CNS as well as peripheral tissues [42].

Due to the dual analgesic and antiinflammatory properties of the FAAH inhibitors, these have been preferably evaluated as a therapeutic approach in preclinical models of inflammatory pain. These models involve the application of harmful substances to the hind leg, resulting in inflammation (edema) and measurable nociceptive behavior, including allodynia and hyperalgesia. FAAH inhibitors have been shown to suppress inflammatory pain induced by formalin [43], carragenin [44] and Freund's adjuvant (CFA) [45].

Both CB1 and CB2 receptors have been implicated in the antinociceptive effects of FAAH inhibition in those models [45,46] and it is likely that CB2 receptor could be more implicated in inflammatory pain since peripheral immune cells and glial cells express mainly this receptor subtype.

The monoacyglycerol lipase (MAGL) was identified as the main enzyme responsible for the degradation of 2-AG [47]. 2-AG is the main endocannabinoid present in CNS [48] and responsible for most of the well-characterized synaptic properties of CB1 activation [49]. In 2009, a highly MAGL-selective compound, JZL184, was developed. Its administration increased the acute thresholds of thermal and mechanical pain in mice. This compound demonstrated antinociceptive effects in peripheral inflammatory [41,50,51] visceral and gastrointestinal pain [52,53], although some side effects, as dependence also were evident.

More recently, a new generation of MAGL inhibitors with more attractive therapeutic profiles have been developed [54]. These compounds produce antinociceptive effects in mouse models of acute and chronic pain with reduced cannabimimetic properties [55]. In a recent publication, blockers of 2-AG metabolism have also shown analgesic efficacy both in inflammatory and neuropathic pain [56].

#### 2.1.2. Receptor modulation

*2.1.2.1. Inflammatory pain.* The use of cannabinoid agonists and antagonists has allowed us to know the different involvement of the cannabinoid system in the pain process. Numerous agonists have been used and tested in different models of acute and inflammatory pain. Recently it has been shown that they play an important role in the modulation of downstream pathways such as RVM in situations of inflammation induced by CFA through GABA modulation [57]. This suggests that selective activation of CB2 receptors may have a therapeutic potential to treat persistent inflammatory pain. An additional benefit is that CB2 receptor agonists have a lower ability than CB1 receptor agonists to induce tolerance and withdrawal effects [58], as well as psychotropic side effects [59].

*2.1.2.2. Muscle pain.* The local administration of different cannabinoid

agonists induces analgesia in a muscle pain model induced by hypertonic serum (HS) [60]. In a masseter pain model, both systemic (intraperitoneal) and local (intramuscular) administration of CB1 and CB2 agonists reduced the nociceptive behavior induced by HS. When SH was administered in the gastrocnemius, local administration of CB agonists was more effective than systemic. This would be in agreement with several reports showing cannabinoid agonists as analgesic drugs in different muscular pain models. Recently Wong et al. [61], using a temporomandibular myofascial disorder model, demonstrated that THC administration decrease NGF levels and suggested that THC could reduce masticatory muscle pain through peripheral CB1 receptors activation. Interestingly, peripheral application of CB1 agonists could be a novel approach to provide analgesic relief without CNS side effects [61].

*2.1.2.3. Osteoarthritis (OA) pain model.* Cannabinoid receptor 2 are also expressed in DRG neurons, including nerves innervating human osteoarthritic synovium, raising the possibility that activation of CB2 receptors might also directly regulate the excitability of nociceptors. Indeed, this possibility has been confirmed in one study of OA related pain in rats [62]. But not only CB1 and CB2 receptors would be involved in the analgesic effect of cannabinoids. CBD, although structurally like THC, is a non-psychoactive cannabinoid with therapeutic potential for the treatment of several types of pain [63–65]. THC- type cannabinoids act on CB1 or CB2 receptors, whereas CBD-type cannabinoids have little binding affinity. The data suggest that the in vitro application of CBD inhibits signaling through GPR55 expressed in osteoclasts [66] and TRP, producing an inhibition in the release of cytokines like TNF-alpha from synovial cells [67]. In this sense and to reduce the adverse effects, a transdermal application of cannabidiol has recently been tested in an OA model in rats [68]. The application of this compound has significantly reduced swelling of the joints, spontaneous pain, infiltration of immune cells and thickening of the synovial membrane in a dose-dependent manner without adverse effects.

## 2.2. Clinical data

For the last 10 years, a growing number of clinical trials have been published with various cannabinoid drugs [69]. The most commonly used cannabinoids are Cannabis, THC, nabilone, cannabidiol and dronabinol, using different forms and routes of administration.

Sativex® is an oromucosal cannabis-based spray combining a CB1 partial agonist (THC) with a cannabinoid system modulator (CBD). It is approved and available for spasticity in multiple sclerosis refractory to conventional treatment in several European countries, including Spain, and Canada. It was approved in Canada in 2005 for treatment of central neuropathic pain in multiple sclerosis, and in 2007 for the treatment of cancer pain, as and adjuvant analgesic in malignant diseases [70]. Nabiximols® is the United States adopted name (USAN) for Sativex® [GW Pharma Ltd, Wiltshire, UK].

Dronabinol (Marinol ©) is the synthetic form of THC, approved by the FDA in 1986 for the treatment of nausea and vomiting caused by chemotherapy and anorexia-cachexia syndrome associated with AIDS. It is marketed in the USA, but not in Europe, and is useful in the control of certain types of pain. Moreover it potentiates the analgesic effect of morphine derivatives. It has also shown beneficial effects on certain symptoms (pain, stiffness, urinary problems) of multiple sclerosis.

Nabilone (Cesamet®) is a synthetic analogue of THC. It is marketed in the United States, Canada, Mexico and the United Kingdom with the same indications as dronabinol. It has demonstrated its efficacy in the management of pain in advanced cancer.

Below we present results of some of the clinical trials that have been conducted with cannabinoid derivatives used as analgesics in different painful pathologies whose origin is not neuropathic or oncological.

### 2.2.1. Fibromyalgia

Fibromyalgia (FM) is a chronic pain syndrome of unknown etiology. The disease is characterized by generalized musculoskeletal pain, fatigue and multiple tender points in neck, spine, shoulders and hips, called trigger points. It is a pathology treated with conventional analgesics but, very often, poorly controlled.

Patients with fibromyalgia often use cannabis with a therapeutic purpose, to treat symptoms of the disease [71,72]. Doctors, in places where its use is legal, such as Netherlands or California, often recommend the use of cannabis to treat musculoskeletal disorders [73,74]. To date, however, there are few clinical trials evaluating the use of cannabinoids to treat the disease.

Researchers from the University of Heidelberg (Germany) evaluated the analgesic effects of oral THC in nine patients with fibromyalgia for a 3 months period. Subjects were daily treated with different doses (from 2.5 to 15 mg) of THC without receiving any other pain medication during the trial. Among participants who completed the trial, all reported a significant reduction in daily-recorded daily pain as well as in electronically-induced pain [75].

In another clinical study, the effect of synthetic cannabinoid nabilone was evaluated. This was a double blind, randomized and placebo-controlled trial. At the end of the study, authors described that nabilone significantly reduced pain in 40 subjects with fibromyalgia, and was well tolerated [76].

More recently, in 2011, researchers from the Research Institute-Hospital del Mar in Barcelona conducted a trial in which they evaluated the associated benefits of cannabis. In the study they enrolled 28 cannabis-treated patients with fibromyalgia and 28 patients with FM who did not use the substance. The authors found that cannabis use was associated with beneficial effects on several of the symptoms of fibromyalgia, including pain relief and muscle rigidity [77].

### 2.2.2. Gastrointestinal disorders

Gastrointestinal disorders include painful functional bowel diseases such as irritable bowel syndrome and inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis. Incidence and prevalence of these intestinal pathologies are increasing over time and in different regions of the world, indicating their appearance as a global disease [78]. While some gastrointestinal disorders can be controlled by diet and drugs, others are poorly treated by conventional approaches. Symptoms of gastrointestinal disorders often include cramping, abdominal pain, inflammation of the large and/or small intestine, chronic diarrhea, rectal bleeding and weight loss. Patients with these disorders often use cannabis for therapeutic purposes [79,80]. In 2011, a study was published with one hundred patients with ulcerative colitis and 191 patients with Crohn's disease [81]. Patients went to the clinic and completed a questionnaire about current and previous cannabis use, socioeconomic factors, history of diseases and use of medications. Authors concluded that cannabis is commonly used for the relief of symptoms among patients with these inflammatory bowel pathologies, particularly among those with a history of abdominal surgery and abdominal pain.

In a recent work, authors conducted a prospective study in which they observed patterns of marijuana use in patients with IBD at a medical center [82]. A total of 292 patients completed the survey; 12.3% of patients were active users of marijuana, 39.0% had ever used. The rest had never consumed. Among those who consumed and had consumed, 16.4% of patients used marijuana to treat the symptoms of the disease. Most of these patients (74.41%) considered marijuana to be "very useful" for relieving abdominal pain.

### 2.2.3. Migraine

Cannabinoids has demonstrated their utility as analgesics in other painful pathologies. In 2009 [83] a case of a patient with cluster headache, refractory to multiple acute and preventive drugs was presented. The patient successfully blocked his attacks with the

recreational use of marijuana; the subsequent use of dronabinol provided equally effective pain relief. Authors attributed the efficacy of cannabinoid in this headache with high concentration of cannabinoid receptors in the hypothalamus.

#### 2.2.4. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an inflammatory disease of the joints characterized by pain, stiffness and swelling, as well as eventual loss of limb function. It is estimated that rheumatoid arthritis affects about one percent of the population, mainly women. Patients with RA often discuss the use of cannabis to treat symptoms. In 2005 an anonymous questionnaire was conducted among Australian patients, indicating that 35% of patients with RA used cannabis to alleviate the symptoms of the disease [84].

Moreover, a survey conducted in the same year in the United Kingdom showed that more than 20% of the respondents who used cannabis for therapeutic purposes did so to treat the symptoms of RA [71]. Numerous preclinical work can be found where the effect of cannabinoids on RA is evaluated, but, to date, few clinical studies have investigated the use of cannabis for RA.

In January 2006, British researchers conducted a controlled trial that evaluated the efficacy of natural cannabis extracts in RA [85]. Sativex administration, for five weeks, induced statistically significant improvements in movement-related pain, rest pain, sleep, inflammation and pain intensity, compared to placebo. No serious adverse effects were observed.

However, in a recent meta-analysis [86] in which the efficacy, tolerability and safety of cannabinoids in chronic pain associated with various rheumatic diseases such as osteoarthritis and rheumatoid arthritis are evaluated, authors conclude that, due to the low quantity and quality of available data concerning efficacy, tolerability and safety of cannabinoids in chronic pain refractory to conventional treatment associated with rheumatic diseases, no current recommendation for routine clinical use can be proposed. They recommend carrying out more randomized controlled trials.

## 3. Neuropathic pain

As a faulty cable may lead to spark discharges even in the absence of a stripped wire, the nerve fibres transmitting pain may also overreact yet there is no visible damage. In this respect, neuropathic pain refers to a nerve tissue ailment either in the peripheral (primary afferent nerve fibres, sensory ganglia and spinal roots) or central nervous system. Multiple evolving symptoms and mechanisms may be present at the same time. An initial lesion can trigger inflammatory responses at the site of the nerve injury and in the spinal projection area. Hence, although neuropathic pain can be acutely caused, it corresponds more frequently to slow adaptive mechanisms in which sort of a chronic neuroinflammatory process is involved [7,8].

In neuropathic pain, circulating immune cells (mast cells, macrophages and T cells), and other immune-like elements can proliferate at the site of injury (e.g.: Schwann cells). Moreover, immune-derived factors might either induce activity in the axons or alter the gene expression of neurons in the dorsal root ganglia. That is, peripheral nerve injuries that lead to neuropathic pain states can cause immune-mediated changes not only in the damaged peripheral nerve and DRG, but also in the CNS [87,88]. In sum, cross-talk between neuroglial cells and neurons modulates the nociceptive stimulus and hence determine the presence or not of hypersensitivity [89].

However despite functioning of neuropathic pain has been depicted in the past years, treatment is still limited by the efficacy and dose-limiting adverse effects of drugs. Current treatment includes the use of anticonvulsivants such as gabapentin and pregabalin, antidepressants such as amitriptyline and duloxetine, the use of certain opioids such as tramadol or, recently, the antiarrhythmic drug mexiletine [90]. That is, neuropathic treatment still has a scarce efficiency and new therapeutic approaches are needed [90].

### 3.1. Data from animal studies

In order to glimpse the potential use of cannabinoids in pain relief, it is necessary to examine previously their effects in animal models. Human endocannabinoid system is not only analogous but homologous in terms of distribution, localization and functioning to that of rodents [23]. Their co-localization in several areas of the CNS and the existence of an analgesic effect despite sharing different molecular pathways, has led to the development of numerous cannabinergic agents for experimental pharmacological use in search for new analgesic alternatives [91]. In this line, cannabinoids have extensively shown acute analgesic properties in different models of neuropathic pain in mice and rats, such as that induced by spinal nerve ligation, diabetes, paclitaxel, vincristine or cisplatin.

Cannabinoids suppress neuropathic nociception through CB1 and CB2 mechanisms. CB1 is predominantly located within the CNS. CB2 is expressed predominantly, but not exclusively in immune cells and, at low levels, in the brain. CB2 is upregulated in DRG and spinal cord following injury. CB2 activation is not associated with CNS side-effects linked to CB1. In animal models, (R,S)-AM1241 (CB2 agonist) suppresses inflammatory, neuropathic and cancer pain. It is now known that animals will self- medicate with a nonpsychotropic analgesic to alleviate spontaneous chronic pain [92]. Recently, special attention is being directed to animal models evaluating spontaneous rather than evoked pain. To this aim, paradigms in which rats self-medicate with a non psychotropic analgesic (CB2 agonist) to alleviate a neuropathic pain state have been studied.

In a model of high-fat diet plus streptozotocin (STZ)-induced type 2 diabetes, central (intrathecal) administration of a CB2-selective agonist (L-759,656) but especially non- selective CB1/CB2 agonist (WIN-55,212-2) dose-dependently reduced heat hyperalgesia. This effect was significantly antagonised by a CB2-selective antagonist (AM630), showing that activation of cannabinoid CB2-receptors in the spinal cord inhibited thermal hyperalgesia in diabetic mice. Since CB1- outnumber CB2-receptors in the brain and given that no change in protein levels of these receptors are observed under such pathological condition induced in mice, analgesia exerted by CB2-receptors outside the brain might be a good target to treat diabetic neuropathy and avoid psychological side effects. Stimulation of CB2-receptors would inhibit the activation of microglia, and hence inhibit neuropathic pain [93].

Noteworthy, peripheral neuropathy is also one of the major adverse effects of chemotherapy, particularly when taxane, Vinca alkaloids or platinum-derived drugs are given. In this line, paclitaxel-induced peripheral polyneuropathy is a well-accepted animal model of neuropathic pain [94]. Distinct mechanisms may underlie the development of neuropathic pain induced by different antineoplastic agents and therefore, treatment could also differ. Pharmacotherapy for antineoplastic-induced neuropathy is limited because the underlying cellular mechanisms remain incompletely understood.

In experimental models, not only the non-selective CB1/CB2 agonist WIN55,212-2 (WIN) suppressed neuropathic nociception induced by paclitaxel through a CB1- specific mechanism [95] but also CB2 selective agonists attenuated neuropathy [96]. Likewise WIN suppressed vincristine-induced neuropathy through the activation of both CB1 and CB2 receptors [97]. Previously, we have demonstrated that WIN prevented the development of mechanical allodynia in cisplatin- [98] and paclitaxel-treated [99] rats. Local administration of WIN was effective to significantly reduce mechanical allodynia in the ipsilateral paw, without modifying the threshold in the contralateral paw in cisplatin-treated rats, suggesting that cannabinoids did not need to reach the CNS to exert an antiallodynic effect at the dose tested. The lack of effect of either WIN or ACEA at 1 mg/kg on the cannabinoid tetrad further suggests that their effect upon intraplantar administration may be due to activation of local CB1 receptors. JWH133 (CB2 selective agonist)

**Table 1**
Principal experimental cannabinoid drugs.

| | Drug | | Synthetic |
|---|---|---|---|
| CB1-receptor agonists | ACEA<br>AZD1940<br>AZD1704<br>AZ11713908 | CB1-receptor antagonists | AM251<br>SR141716A |
| CB2-receptor agonists | AM-1241<br>AM-1710<br>GW405833<br>HU308<br>JWH-133<br>L759,656<br>NESS-400 | CB2-receptor antagonists | AM630<br>SR144528 |
| CB1/CB2-receptor agonists | AEA<br>CP55,940CT-3 (ajulemic acid)<br>Dronabinol<br>LBP-1<br>naphtalen-1-yl-methanone<br>WIN-55,212–2 | CB1/CB2-receptor antagonists | – |

was capable of reducing mechanical allodynia when topically administered. Non-psychoactive doses of non-selective agonist WIN55,212-2, CB1-selective agonist ACEA or CB2-selective agonist JWH133 were administered in cisplatin-treated rats. Also selective CB1 (AM251) and selective CB2 (SR144528) antagonists to discriminate CB1 or CB2 mediated effects. Local and systemic administration of CB1-selective agonists but apparently only systemic administration of CB2-selective agonists can alleviate allodynia in cisplatin- induced neuropathy. However, cisplatin-treated rats showed mechanical allodynia but not thermal hyperalgesia. Mechanical allodynia was alleviated through both CB1 and CB2 receptor activation when the cannabinoid was systemically applied. On the contrary, activation of peripheral CB1 seemed to have an effect when locally applied, but not when peripheral CB2 was activated [100].

In a neuropathic pain model induced by partial sciatic nerve ligation or a spared nerve injury, both local and systemic administration of CB2-selective agonists, JWH-133 but especially beta-caryophyllene (BCP), NESS400, AM1241 and GW405833, showed to dose-dependently attenuate mechanical allodynia and thermal hyperalgesia (Table 1). Importantly, BCP is also analgesic when orally given. Reduced spinal neuroinflammation, that is, diminished expression of microglia and astroglia markers and reduced proinflammatory cytokines and chemokines in the dorsal horn of lumbar spinal cord, was also observed. Thermal hyperalgesia and mechanical allodynia, which are mediated by different nociceptive neurons, appeared to be differently affected by CB2 agonism [5,101].

The most restricting issue for clinical use is CB1-mediated cannabimimetic effects. Low-dose systemic administration of a non-selective CB1/CB2-receptor agonist (CP- 55,940) in a mouse model of neuropathy produced by paclitaxel suppressed allodynia in wild type and CB2KO mice, but not in CB1KO mice, whereas high dose produced catalepsy in wild type and CB2KO mice but in CB1KO mice just suppressed allodynia with no additional effects. Therefore, CB1 and CB2 receptor activation produce mechanistically distinct suppression of neuropathic pain. Moreover, these antiallodynic effects were blocked by the CB2 antagonist AM-630. Apparently, since CB1-receptors outnumber CB2-receptors in the CNS, CB2-mediated antinociceptive effects are probably being masked by CB1-mediated catatonia associated with mixed cannabinoid agonists. Activation of spinal and/or peripheral CB2 receptors by CB2 agonists, after acute or chronic administration, suppresses neuropathic pain [102].

**Table 2**
Drugs used in clinical trials and clinics.

| | Drug | Medicine |
|---|---|---|
| CB2-receptor agonists | Cannabichromene<br>cannabigerol<br>Tetrahydrocannabivarin | – |
| CB1/CB2-receptor agonists | CBD (cannabidiol)<br>Dronabinol<br>Levonantradol<br>Nabilone THC | Cesamet (nabilone)<br>Marinol<br>(THC + dronabinol)<br>Sativex (THC + CBD)<br>Nabiximols (THC + CBD) |

### 3.2. Clinical data

As previously mentioned, different cannabinoids may induce mechanistically different pain relieving effects [103]. Guidance and assays on cannabinergic drugs prescription for patients with severe neuropathic pain conditions are still scarce and reduced in size. In Canada, preliminary works have been carried out in this respect [104], however evidence and safety reports are still limited. To date cannabinoids are still considered as a second- line treatment of pain since more studies on safety and therapeutic efficacy are needed [105,106].

A major concern with the use of CB1-selective drugs is the risk of associated serious psychotropic side effects. By way of example: the European Medicines Agency (EMA) withdrew rimonabant (SR-141716A) from the market, a selective CB1-receptor antagonist, two years after being approved for its clinical use in 2006 for inducing depression, anxiety and suicide tendency [107]. Despite, CB1-mediated response inhibits nociceptive responses in a higher degree than CB2, stimulation of CB2-receptors also suppresses both inflammatory and neuropathic pain with little or no effect on psychological functions.

All the three cannabis-based medicines commercially available (Table 2) correspond to non-selective CB1/CB2 agonists (mainly THC or derivative) and can be used for the treatment of neuropathic pain, counting on nausea and dizziness as major side effects. In the past years, quite a few number of clinical trials have endeavored to envisage a putative analgesic effect in neuropathic syndromes mediated by cannabinoid drugs. Comparative studies between nabilone and gabapentin, for instance, suggest a similar effect in providing analgesia in patients with peripheral neuropathy [108]. Significant pain relief has also been seen when Sativex is oromucosally administered in patients refractory to conventional treatments compared to placebo [109]. Oral dronabinol, a synthetic analogous of THC, has proven effective in reducing pain intensity in patients with multiple sclerosis [110,111]. And recently, nabiximol, an oromucosal spray containing THC, CBD and minor cannabinoids and terpenoids, has been used in a trial of chemotherapy-induced neuropathic pain. However, the study reports significant individual variations. One possible reason for this situation might be that subjects included in this study followed paclitaxel, vincristine or cisplatin chemotherapy indistinctly [112].

Similar to the studies carried in basic research, systematic reviews on clinical trials suggest that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions [113,114].However they are cautious on prescription and indicate their use only in patients refractory to conventional therapy.

## 4. Cancer pain

Over 10 million people are diagnosed with cancer every year across the world and nearly half of them are notoriously undertreated [115]. Cancer pain can be of a varied aetiology, ranging from the cancer process itself –in which the tumour compresses the surrounding tissues, organs or nerves– to surgical postoperative pain, or even chemo- or radiotherapy-induced peripheral neuropathy.

In 1986, the World Health Organization (WHO) presented a three-

step analgesic ladder to serve as guidance on the management of cancer pain. Thirty years later this framework still stands as a highly effective guidance for providing satisfactory analgesia to most patients suffering from cancer pain (71–86%), being non-steroidal anti-inflammatory drugs (NSAID) and opioids the drugs most commonly used [116,117]. However, under certain circumstances these analgesics fail to achieve satisfactory analgesia, particularly at higher doses due to opioid-specific risks or because of intolerable side effects.

Cannabinergic pain medicine –including both cannabis and cannabinoids– is becoming a therapeutic alternative for cancer patients refractory to commonly available medications [118,119], such as those with opioid resistant pain [120].

Current literature on the use of cannabinoids in cancer pain has provided controversial results [121].

### 4.1. Data from animal studies

Preclinical studies have been performed to study the modulation of cancer pain by different cannabinoids with affinities by CB1 and CB2 receptors and the possible synergism effect with other drugs. The most of the reported results come from bone cancer pain animal models. There are data suggesting a role for CB1 receptors, but not for CB2 receptors, on the deep tissue hyperalgesia on a bone cancer model in mice [122]. In a fibrosarcoma cancer pain model, both CB1 and CB2 receptor agonists reduced the mechanical hyperalgesia induced by the tumor [123]. Nevertheless, there is also evidence implicating the role of the CB2 receptor in two different types of painful bone tumours pain in mice (injection of NCTC 2472 osteosarcoma or B16-F10 melanoma cells) where CB2 agonists diminished the thermal hyperalgesia and mechanical allodynia induced by the tumors [124].

A number of preclinical studies have demonstrated that the skeletal CB2 receptor plays a role in the regulation of tumor-bone cell interactions and preclinical studies showed that pharmacological targeting of CB2 is effective in reduce skeletal tumor burden, inhibiting osteolysis and attenuating bone pain in an animal model of osteolytic bone disease (review [125]).

Some studies have also demonstrated the antinociceptive efficacy of peripheral cannabinoid agonists in reducing the painful behaviors [126,127]. Local administration of WIN 55,212-2 (CB1/CB2 non-selective) or AM1241 (CB2 selective agonist) was capable of reducing hyperalgesia in the squamous cell carcinoma [128] and in the fibrosarcoma bone cancer murine models [129].

There is also evidence that cannabinoids may act synergistically with opioids. Part of this is related to a direct synergistic analgesic effect since CB1 and CB2 receptor agonists promote analgesia in a murine model of tumor pain [123]; moreover, cannabinoids may reduce or prevent opioid tolerance, a process that may also be mediated by the CB2 receptor [130].

In relation to endogenous cannabinoids it is well known that also play a crucial role in cancer pain. Local injection of anandamide and an inhibitor of FAAH reduced mechanical hyperalgesia induced in a osteolytic bone model [131].

However, although animal studies help to understand the effects and mechanisms mediated by cannabinoid receptors using selective agonists and antagonists, these results are not translational to the clinical settings.

### 4.2. Clinical data

All clinical trials aimed to assess the efficacy of cannabinoids in cancer pain are based on the use of cannabis derivatives. Given that neuropathic pain is most frequent in cancer patients, the efficacy of these compounds in the former will make them suitable as cancer pain medications [132,133].

Out of the eleven existing trials on cancer pain and cannabinoids [134], eight have already been completed. The compounds tested in the trials consist in: smoked cannabis, Nabiximols or Sativex (THC:CBD oromucosal spray) and THC alone. The most relevant outcome from such randomised, double-blind and placebo-controlled studies are:

– A comparative study of Sativex (THC:CBD extract) versus THC alone showed greater efficacy in pain relief in favour of the former in patients with advanced cancer pain not fully relieved by strong opioids. The proportion of responders was 43%, 23% and 21% in Sativex, THC and placebo groups, respectively [135].

Cannabinoids may increase the risks of adverse effects despite their potential efficacy in pain relief, and these are responsible for not all patients who begin the study to complete it; It is noteworthy that in all clinical trials sample is lost over time, often due to the low tolerance shown by patients to the side effects (somnolence, dizziness, confusion and nausea).

– Some years later, in another study, the long-term use of THC:CBD spray showed be generally well tolerated without any loss of analgesic efficacy for pain relief [136].
– Nabiximols may be a useful add-on analgesic option for patients with opioid- refractory cancer pain. A graded-dose study with a total sample size of 360 patients demonstrated efficacy and safety at low and medium doses [137].
– Sativex was not superior to placebo when given as adjuvant therapy in advanced cancer patients with opiate-resistant chronic pain [138].
– Nabiximols given as adjuvant therapy did not show any analgesic benefits compared to placebo in advanced cancer patients with chronic uncontrolled pain but it did improve their life quality [139].

Taking together, the results obtained from clinical trials suggest no strong argument to indicate the use of cannabinoid extracts for the treatment of cancer pain. However, cannabinoids do improve the quality of life and sleep of the patient, which could represent an alternative adjutant use for certain patients.

Current clinical trials being performed at present are evaluating the efficacy and safety of inhaled medical cannabis at different concentrations of CBD and THC. A novel oral delivery of oil-based formulation (MRCP001) is also being analysed in cancer patients with undermanaged pain. No studies on the use of smoked cannabis in cancer pain have been conducted so far. However, medical marijuana legalization in Canada and certain states of the United States will surely soon provide physicians with new information for a proper prescription in cancer pain [118].

Additionally, dronabinol and nabiximols might be considered interesting options for reducing nausea and vomiting in chemotherapy-treated patients [140].

Recently, the results of a survey carried out by the European Pain Federation (EFIC) on the availability and approval of cannabis-based medicines for chronic pain management and palliative/supportive care in Europe have been made public. Naturally-derived dronabinol (an isomer of THC) is approved for cancer pain in Denmark and Croatia, as well as in Israel. The study is meant to serve as a guidance that provides general recommendations such as: 1) plant-based and synthetic cannabinoids should be reimbursed by health insurance companies in patients with chronic pain refractory to conventional treatment and patients with cancer pain; 2) cannabinergic drugs should not be used as a first- or second-line therapy; 3) rather than in monotherapy, cannabinoids should be prescribed as part of a multimodal therapy or a multidisciplinary program; 4) smoked cannabis should not be recommended for ultimately leading to detrimental health [141].

## 5. Conclusions

Cannabinoids have demonstrated antinociceptive effects in several

preclinical models of acute, inflammatory, neuropathic and cancer pain. These effects are evident using both CB1 and/or CB2 agonists.

Cannabinoid agonists can produce antinociception through central and peripheral mechanisms and suppress central sensitization in spinal dorsal horn neurons in neuropathic pain models.

At least in some kinds of pain, a mixed CB1/CB2 agonist may be more effective than CB1 or CB2-selective agonist, however unwanted psychotropic effects still present.

CB2 agonists are likely to suppress neuropathic nociception by downregulation of proinflammatory cytokines and chemokines as well as inhibition of central sensitization.

Cannabinoids might be useful in situations when pain does not resolve with opioids, albeit additional clinical trials are needed before supporting the use of cannabinoids as analgesics in different types of pain, considering the low quality of evidence in a majority of studies.

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