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## Medicinal cannabis products for the treatment of acute pain

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### Abstract

For thousands of years, medicinal cannabis has been used for pain treatment, but its use for pain management is still controversial. Meta-analysis of the literature has shown contrasting results on the addition of cannabinoids to opioids compared with placebo/other active agents to reduce pain. Clinical studies are mainly focused on medicinal cannabis use in chronic pain management, for which the analgesic effect has been proven in many studies. This review focuses on the potential use of medical cannabis for acute pain management in preclinical studies, studies on healthy subjects and the few pioneering studies in the clinical setting.

**Key Words:** Cannabis; Cannabinoids; Endocannabinoid system; 2-arachidonoylglycerol; Anandamide; Analgesia; Acute pain

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**Core Tip:** Medicinal cannabis use for pain management is still controversial. Meta-analysis of the literature has shown contrasting results on the addition of cannabinoids to opioids to in reducing pain. Clinical studies are mainly focused on medicinal cannabis use in chronic pain management, for which the analgesic effect has been proven in many studies. This present review focuses on the potential application of medical cannabis for acute pain, exploring the physiopathology of the endocannabinoid system, preclinical studies, studies on healthy subjects and the few pioneering studies in the clinical setting.

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## INTRODUCTION

The definition “medicinal cannabis” identifies the prescription-based cannabis and cannabinoids recognized to treat, modulate or even extinguish signs and symptoms of disease[1].

At the moment its prescription is limited to certain rare clusters of patients such as forms of drug-resistant adult or pediatric epilepsy, third-line antiemetic agents in chemotherapy-treated patients, and spasms in the context of multiple sclerosis (MS). There is some evidence medical cannabis can help certain types of pain, though this evidence is not yet strong enough to recommend it for pain relief[2]. Pain is “an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage”, the International Association for the Study of Pain in the last revision of the pain definition pointed out the concept of the protective role of acute pain in contrast with the maladaptive nature of chronic pain[3]. Acute pain serves as a warning sign of disease or threat to the body; It happens suddenly, starts sharp or intense, is caused by injury, surgery, illness, trauma, or painful medical procedures and generally lasts from a few minutes to less than six months. Acute pain usually disappears whenever the underlying cause is treated or healed[4].

The burden of acute pain worldwide is remarkable and covers 4 out of 10 patients admitted yearly to the Emergency Department (ED)[5]. Their improper/inefficient therapeutic management is capable to cause several hospital new admission and even consolidate a life-long chronic pain status[6]. Their evolution toward pain chronicity is also testified by the opioid use/misuse of these patients in the previous three 3 months, quantified in a recent report regarding 1 out of 5 patients[7].

Remarkably, patients with chronic pain treated with opioids have a higher risk of opioid overdose[8], in particular, the United States population with opioid use disorder was quantified in 1.6 million last year[9]. Even more dramatic are the 30 years of survey data that found 564 thousand patients perished from opioid (medical and illicit) fatal overdoses[10]. In this respect, a multimodal approach to acute pain management with the use of non-opioids medication should be mandatory. This review aims to evaluate medicinal cannabis products for the treatment of acute pain from the physio-pathological rationale to the more recent clinical practice.

## THE PHYSIOPATHOLOGICAL RATIONALE FOR THE USE OF CANNABINOIDS IN ACUTE PAIN

The endocannabinoid system (ECS) plays a vital role in managing pain by adjusting the activity of various neurotransmitters and receptors that are involved in the sensation of pain. The ECS is composed of endocannabinoids (such as anandamide and 2-arachidonoylglycerol), their receptors (CB1 and CB2), and numerous enzymes that are responsible for both the synthesis and the degradation of endocannabinoids.

The ECS can modulate multiple pathways involved in the perception of pain. Two primary endocannabinoid receptors, CB1 and CB2, have been identified as being involved in the pathophysiology of acute pain.

The CB1 receptor, which belongs to the family of receptors that are coupled to G-proteins, transmits signals through the release of G $\beta\gamma$  proteins and the decrease of cAMP orchestrated by G $\alpha_i$  in the regulation of neurotransmission, neurodevelopment, and synaptic plasticity[11].

Once activated and dissociated these proteins are modulated by a kinase through a series of interactions mediated by  $\beta$ -arrestins[12].

CB1 receptors are expressed in higher concentration in the central nervous system (CNS), and modulate the release of neurotransmitters, acting as gatekeepers at the pre-synaptic terminals of GABAergic and glutamatergic neurons[13].

Furthermore, these receptors are dispersed throughout the cell, including areas such as lipid rafts, endosomes, and mitochondria. They can also be found in cells such as astrocytes and oligodendrocytes, as well as in various non-neural tissues such as the heart, lungs, and bones. These peripheral receptors are involved in the control and modulation of nociceptive sensitivity, peristalsis, reproduction, energy and muscle metabolism[14].

CB1 receptors have a vital function in controlling the experience of pain by managing the conversion of harmful peripheral stimuli into pain signals at the spinal cord level. They are capable of both diminishing or intensifying the transmission of pain signals to the CNS.

CB1 receptors located in higher brain regions (periaqueductal gray matter and rostral ventromedial medulla) are linked to the perception of pain, initiating the descending inhibition of pain signals or hindering the descending facilitation to the nociceptive circuit of the spinal cord[15].

Furthermore, CB1 is highly expressed in the brain regions related to the emotional and affective aspects of pain in humans, like the frontal-limbic circuits. It's mainly located on the presynaptic terminals of neurons and concentrated in the perisynaptic zone where it can regulate the neurotransmitter release. This mechanism aligns with CB1's role in retrograde neurotransmission, and it's becoming an increasingly important area of research in pain management[16].

CB1 receptors are coupled negatively, by Gi/o proteins, to the enzyme adenylate cyclase.

When activated, the CB1 receptors inhibit the calcium channels and activate the potassium channels, which decreases neurotransmitter release[17].

However, this is a synthetic description of the role of CB1 receptors. *In vivo*, the overall effect of CB1 receptors activation differs within the neural network according to the areas of the brain and the type of presynaptic cell involved in the pain pathway.

CB1 receptors have been found even in B immunity cells and the CNS's glial cells. In the CNS astroglial CB1 receptors play a crucial role in regulating behaviour and plasticity[18].

The CB2 receptor is mostly linked to Gi/o proteins and is involved in signalling pathways that regulate intracellular calcium concentration. Unlike CB1 receptors, the CB2 receptor is not commonly found in the CNS, but it is highly expressed in immune system cells both peripheral (macrophages, lymphocytes, and mast cells).

The activation of CB2 receptors reduces especially inflammatory pain states by anti-inflammatory effect and the reduction of hyperalgesia[17].

There is an ongoing debate about the presence of active CB2 receptors in the CNS, especially in astrocytes and microglia, but the evidence remains inconclusive. **Figure 1** offers a synthesis of the distribution of the ECS receptors in the CNS, in the spinal cord and the peripheral nervous system. The receptors expressed in the CNS (mostly CB1) are involved in the modulation of the descending control of nociception and in the emotive perception of pain.

The receptors located in the dorsal horns of the spinal cord have a role in pain ascendent sensitive nociception pathways. The receptors expressed in the peripheral nervous system contribute to the excitability of nervous termination and modulate the immunity system through the immunity cells sensible to endocannabinoids.

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## THE USE OF CANNABINOIDS FOR ACUTE PAIN IN PRECLINICAL STUDIES

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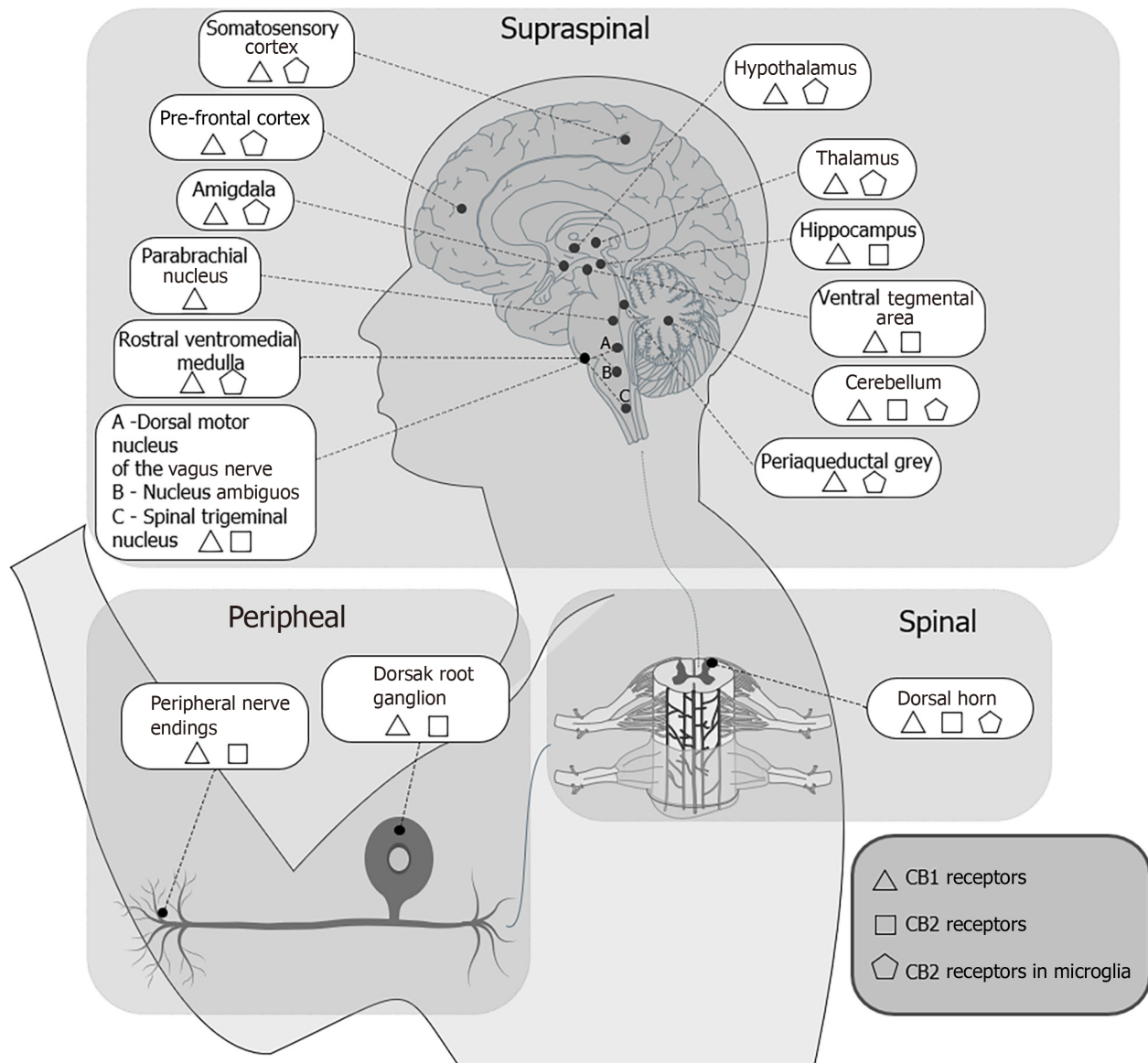
For half a century cannabinoids have been evaluated for their analgesic effect in animal models[19]. In 1973 Sofia *et al*[19] evaluated the analgesic properties of tetrahydrocannabinol (THC) in mice and rats using four different models of experimentally induced pain (Acetic acid-induced abdominal constriction, Haffner's tail pinch, Hot plane test, Randall-Selitto test); THC, in all the models studied, showed greater analgesic activity than aspirin. In 2002 Conti *et al*[20] evaluated the anti-inflammatory action of the synthetic cannabinoid nabilone in a model of acute inflammation (AI) in male Wistar rats: The anti-inflammatory activity and thermal hyperalgesia were explored respectively by measuring oedema and paw withdrawal latencies, using the radiant heat method, after the injection of 0.1 mL carrageenan into the right paw. Paw oedema and thermal hyperalgesia were modulated by nabilone in a dose-dependent manner. Likewise, the CB2 antagonist (SR 144528) pre-administered neutralized the nabilone effect. The authors concluded the effect of nabilone is mediated by an uncharacterized CB<sub>2</sub>-like cannabinoid receptor[20]. More recently, Rock *et al*[21] evaluated the effect of cannabidiolic acid (CBDA) and Δ<sup>9</sup>-THC in a similar rodent model of carrageenan-induced AI in the rat hind paw. Contrary to the previous study the authors used a CB<sub>1</sub> cannabinoid receptor antagonist (SR141716) to block the anti-hyperalgesia effects of THC while CBDA's effects were blocked by a competitive and selective vanilloid receptor 1 (AMG9810). Consistent with previous literature (Conti *et al*[20]), Rock *et al*[21] demonstrated that THC produced dose-dependent anti-hyperalgesia and anti-inflammatory effects and they are further synergic use of CBDA. CBDA contrasts hyperalgesia *via* vanilloid receptor 1, as testified by its selective inhibition with AMG9810, conversely THC acts on central and peripheral CB1 receptors, as testified by its selective inhibitor SR141716[21].

Cannabinoids improve pain in pre-clinical models of traumatic spinal cord injury (SCI)[22]. SCI causes Neuropathic pain (NP) with different mechanisms, one of which involves oxidative stress. Baron-Flores *et al*[23] established the biomechanism by which CBD may exert a powerful analgesic effect in acute NP: In fact, CBD empowers the natural anti-oxidative cellular defence such as glutathione concentration in a dose-dependent manner. Thus, cells experienced decreased lipid peroxidation (Table 1).

**Table 1** Synthesis of a selection of the preclinical studies published on acute pain treatment in preclinical studies

Ref.	Animal	Cannabinoid	Model	Outcome(s)	Assessment
Conti <i>et al</i> [20], 2002	Wistar rats	Nabilone	Cg-Induced AI	PWL	1, 2, 3, 10 h
Rock <i>et al</i> [21], 2018	Sprague-Dawley rats	CBDA, THC	Cg-Induced AI	PWL	0.5, 1, 3, 6 h
Baron-Flores <i>et al</i> [23], 2022	Wistar rats	CBD	Traumatic SCI	LP & GSH	15 d

Cg: Carrageenan; AI: Acute inflammation; PWL: Paw withdrawal latency; CBD: Cannabidiol; CBDA: Cannabidiolic acid; THC: Δ9-tetrahydrocannabinol; SCI: Spinal cord injury; LP: Lipid peroxidation; GSH: Glutathione concentration.



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**Figure 1** Distribution of the endocannabinoid system receptors in the CNS. CB: Cannabinoid; CNS: Central nervous system.

## THE USE OF CANNABINOIDS FOR ACUTE PAIN IN HEALTHY SUBJECTS

Unlike preclinical studies that showed the efficacy of cannabinoids in acute pain, the results on healthy volunteers (HVs) do not appear to confirm the potential analgesic effect of medicinal cannabis products for the treatment of acute pain. Kraft *et al*[24] demonstrated that THC has no analgesic and antihyperalgesic effects in two human models of physically-induced and chemically induced pain.

**Table 2 Synthesis of a selection of studies published on acute pain treatment in healthy subjects**

Ref.	Number	Cannabinoid (dose)	Model(s)	Outcome(s)	Assessment
Kraft <i>et al</i> [24], 2008	18	THC 20 (mg PO)	Sunburn; Capsaicin ID	Heat and electrical thresholds	1, 2, 2.5, 3, 4, 5, 6, 7, 8 h
Schindler <i>et al</i> [25], 2020	11	THC (0.01 mg/Kg or 0.03 mg/Kg IV)	Capsaicin ID	VAS; HA; Heat and electrical thresholds	0.3; 2 h
Schneider <i>et al</i> [26], 2022	20	CBD (800-mg PO)	IES	NRS; vFF; DCS	0, 1, 2.1 h
Dieterle <i>et al</i> [27], 2022	24	CBD (1600-mg PO)	IES	NRS; HA; AA	1 h

THC: Δ 9-tetrahydrocannabinol; PO: *Per os*; ID: Intradermally; IV: intravenous; VAS: Visual analogue scale; HA: Hyperalgesia Area (cmq); CBD: Cannabidiol; IES: Intradermal electrical stimulation; NRS: Numeric rating scale; vFF: von Frey filament; DCS: Dry cotton swab; AA: Allodynia area (cmq).

**Table 3 Synthesis of a selection of studies published on acute pain treatment**

Ref.	Patient number	Cannabinoid (dose)	Participants	Conclusion
Beaulieu[28], 2006	41	Nabilone (1 or 2 mg PO)	Major surgery	Pain higher in 2 mg group
Ostenfeld <i>et al</i> [29], 2011	123	GW842166 100 and 800 mg	Extractive surgery	Not superiority to placebo
Bebee <i>et al</i> [30], 2021	100	CBD (400 mg)	LBP	Not superiority to placebo

PO: *Per os*; CBD: Cannabidiol; LBP: Low back pain.

In line with the previous study, also Schindler *et al* colleagues that did not find any THC analgesic and antihyperalgesic effect of THC administered intravenously[25].

In a randomized, placebo-controlled, double-blinded, crossover study (CANAB I), Schneider *et al*[26] colleagues did not find any effect of oral CBD on hyperalgesia and allodynia electrically induced, results conformed in the CANAB II trial doubling CBD dose used in CANAB I trial[27] (Table 2).

## THE USE OF CANNABINOIDS IN CLINICAL STUDIES

Beaulieu *et al*[28] colleagues performed a double-blind, randomized, placebo-controlled, parallel-group pilot trial enrolling forty-one patients undergoing major surgery, mainly gynecologic (46%) or orthopaedic (44%). Patients were randomly assigned to four distinct groups (nabilone 1 mg/die Vs nabilone 2 mg/die Vs ketoprofen 50 mg/die Vs placebo). Despite no differences were detected in terms of 24-h morphine request, interestingly the pain control was statistically significant only in the nabilone 2 mg/die.

Conversely, Ostenfeld *et al*[29] did not find a statistically significant analgesic effect of a single dose of GW842166 (non-cannabinoid CB2 agonist) in patients that underwent dental surgery (third molar surgery). Furthermore, this randomized controlled trial (RCT) only re-affirm the high effectivity of ibuprofen Versus placebo[29]. Furthermore, Bebee *et al*[30] colleagues in their RCT focused on low back pain in patients admitted to ED and evaluated the potential efficacy of 400 mg oral CBD as a combination therapy with the department's standard of care. Pain assessment was performed with a verbal scale rating from 0 to 10 their residual pain after two hours from the therapies. This RCT failed to find a clinically relevant decrease in pain comparing patients that underwent CBD+pain killer vs pain killer alone (Table 3).

## CONCLUSION

This is the first review of the literature exploring cannabis products use from preclinical to clinical studies. Mice models have highlighted the analgesic properties of cannabinoids[20,21,23] capable to interrupt pain through partially unknown mechanisms targeting the ECS.

In light of the fact that all studies conducted on HVs failed to show the significant efficacy of medicinal cannabis products for acute pain management[24-27], it seems paradoxical that studies have been conducted on patients[28-30]. To date, the use of cannabis products in the treatment of acute pain is clearly disadvantageous compared to available therapeutic alternatives.

Methodologically phase II clinical trials should follow phase I studies when these latest show efficacies. In the case of studies published on the use of medicinal cannabis products for acute pain induced in HVs, no one showed superiority to a placebo so there is no support to conduct phase II clinical trials. Acute pain management in this Era of the “Opioid Crisis” should not deprive itself of a potential therapeutic option[31]. The knowledge of this review should be taken into consideration by researchers before proceeding further with phase II clinical trials, the researchers should take a “step back” to identify effective models for the treatment of acute pain in phase I studies.

## FOOTNOTES

**Author contributions:** This review was mainly written by Fiore M, Alfieri A and Di Franco S; Alfieri A and Di Franco S collected the data; Pace MC supervised the writing of the paper; Petrou S and Damiani G critically revised the paper; Petrou S provided to revise the English language of the manuscript; and all authors approved the final version to be published.

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