Is There Any Clinically Relevant Cannabinoid-Induced Analgesia?

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Key Words

Cannabinoids • Analgesia • Chronic and acute pain

Abstract

Cannabis sativa is one of the oldest crops cultivated for the production of fibers and for medical and recreational purposes. Since the detection of specific cannabinoid receptors and their physiological ligands, the understanding of the cannabinoid signalling system has increased, leading to a recent resurgence of interest in its medicinal properties. In animal studies, cannabinoids exerted significant analgesic and antihyperalgesic effects, suggesting the usefulness of cannabinoids in pain conditions. However, in human experimental or clinical trials, no convincing reduction of acute pain was observed. In contrast, in chronic pain and (painful) spasticity, an increasing number of randomized, double-blind, placebo-controlled studies have shown some efficacy of cannabinoids. Besides pain, cannabinoids consistently improved mood, sleep and coping. Although cannabinoids are not first-line analgesics, they may be useful adjuvants for some special groups of patients.

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Introduction

Cannabis sativa is one of the oldest crops and has been cultivated for more than 4,000 years for the production of fibers and for medical and recreational purposes. The earliest written reference to it is found in the 15th century BC Chinese pharmacopeia, the 'Rh-Ya'. In Central Asia, India and the Middle Eastern region, the use of cannabis preparations for headache, abdominal pain and cramps was popular and part of the folk medicine.

In the late 18th century, the medical use of cannabis or 'Indian hemp' was reintroduced to Western medicine by the British physician William O'Shaughnessy, who had recognized its therapeutic value during his work in Calcutta. Even Queen Victoria was prescribed cannabis by her physician for the treatment of her menstrual pain. Plant extracts were used in Europe and the USA for the treatment of rabies, tetanus, convulsions, menstrual cramps and headache and were even part of the US pharmacopeia until 1942. Today, only Δ^9 -tetrahydrocannabinol (THC; Marinol®, dronabinol), Nabilone®, a synthetic analogue of THC, and an oromucosal spray containing THC and cannabidiol [cannabis-based medicine (CBM); Sativex®] are approved in several countries and available for medical purposes.

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Modern cannabis research began when, in 1964, the chemical structure of the main psychotropic compound THC was identified by Rafael Mechoulam and his co-workers. Up to now, more than 66 different natural cannabinoids have been isolated from *C. sativa*.

The next significant breakthrough in cannabinoid research was the identification [1] and cloning [2] of the first specific binding site for cannabinoids in the brain, the cannabinoid receptor type 1 (CB₁R), followed by the CB₂ receptor (CB₂R) 3 years later [3]. Through the detection of the physiological ligands of the cannabinoid receptors in 1992, the so-called endocannabinoids, a new signalling system was discovered that is involved in numerous biological pathways. The term 'endocannabinoid system' was established to describe the cannabinoid receptors, their physiological ligands and the enzymes and proteins that regulate their concentrations in the blood and various tissues. Since the discovery of the endogenous cannabinoid system, the increasing information on its physiological role and its contribution to pathology has opened new avenues for the understanding and treatment of various diseases, including pain, addiction, cancer and neurodegenerative and metabolic disorders.

The Endogenous Cannabinoid System

Similar to opioid receptors, the cannabinoid receptors CB₁R and CB₂R belong to the G-protein-coupled receptor family and are embedded in the cell membrane. The binding of a ligand at the cannabinoid receptor site affects second messenger enzymes, mainly leading to the inhibition of adenylate cyclase, blockade of several voltage-gated Ca²⁺ channels [4, 5] and activation of mitogen-activated protein kinase and several K⁺ channels. The CB₁R is mainly expressed in the central nervous system (CNS) and on peripheral neurons but is also present in many peripheral organs and tissues, i.e. liver, testis, small intestine, fatty tissue and endothelium. The CB₂R is mainly expressed by lymphoid organs and cells of the immune system, but under pathological conditions such as neuro-inflammatory diseases, it is also expressed by microglia cells in the CNS. Microglia are derived from macrophages and can be viewed as the resident immune cells of the brain. Some cannabinoid effects could not be explained by CB₁R or CB₂R activation, so the existence of other cannabinoid receptors (CB₃, GPR55) was postulated. Recently, there has been growing evidence that the orphan receptor GPR55 is a functional part of the endocannabinoid signalling system [6].

Endogenous cannabinoids are derivatives of arachidonic acid and belong to the eicosanoid signalling network.

The best characterized endocannabinoids are arachidonylethanolamide (anandamide; AEA) and 2-arachidonoylglycerol. AEA was the first to be isolated from porcine brain in 1992 [7] and is the most important and best investigated endocannabinoid. Named according to the Sanskrit word 'ananda' (bliss), AEA is found in brain, plasma and numerous peripheral tissues.

In the central and peripheral nervous system, endocannabinoids work in a manner similar to neurotransmitters; in other tissues, they can also affect cell functions directly comparable to hormones. However, in contrast to other neurotransmitters, endocannabinoids are not stored in vesicles of nerve terminals; i.e. AEA is formed by the enzymatic cleavage of a phospholipid precursor in the cell membrane by a specific phospholipase D. After its release, AEA signalling is terminated by cellular uptake and rapid enzymatic degradation by the fatty acid amide hydrolase.

In the central and peripheral nervous system, endocannabinoids act as modulators of neurotransmitter release and synaptic transmission. CB₁Rs are located primarily at the presynaptic terminals of central and peripheral neurons, where they mediate inhibition of ongoing release of excitatory and inhibitory neurotransmitters like dopamine, acetylcholine, noradrenaline, glutamate, D-aspartate, 5-hydroxytryptamine and γ -aminobutyric acid by a negative feedback mechanism.

Cannabinoid receptors and endocannabinoids are present in pain circuits from the peripheral sensory nerve endings up to the brain. The distribution of CB₁Rs has been mapped by autoradiographic studies, immunohistochemical techniques, in situ histochemistry and electrophysiological studies. CB₁Rs are 10 times more abundant than μ -opioid receptors in the brain. They are expressed in the hippocampus, basal ganglia, hypothalamus, some areas of the cortex, cerebellum and nucleus accumbens. CB₁Rs are also present in additional areas like the pituitary gland (temperature regulation, endocrine and reproductive function), the amygdala (emotion and fear conditioning) and the nucleus of the solitary tract (nausea and vomiting) [8–10]. There is only a very low expression in brainstem cardiopulmonary centres, explaining the lack of respiratory depression by cannabinoids.

CB₁Rs are also expressed in brain areas involved in nociceptive perception, such as the periaqueductal grey and the rostral ventrolateral medulla, and they co-local-

ize with opioid receptors. CB₁Rs are also present in the substantia gelatinosa of the spinal cord, receiving nociceptive input from primary afferent neurons, which are key sites for modulating nociceptive information. In the medulla oblongata and spinal cord, CB₁Rs are mainly expressed in the superficial dorsal horn and in the dorsolateral funiculus. However, there is some evidence from animal experiments that CB₂Rs are also involved in the antinociceptive effects of cannabinoids.

Cannabinoids for the Treatment of Pain: Preclinical and Animal Studies

Numerous animal studies have revealed that endocannabinoids such as AEA, naturally occurring THC and synthetic cannabinoids like WIN 55,212-2 or CP 55,940 effectively block pain responses in virtually every pain model tested [11–17]. In models of acute pain, cannabinoids were effective against thermal, mechanical and chemical pain and were comparable to opioids in their potency.

In animal models of chronic pain, cannabinoids exhibit a strong analgesic potency, especially in neuropathic and inflammatory pain. The analgesic effects were independent of the route of administration (e.g. oral, intravenous, intrathecal, intraperitoneal). To a certain extent, the behavioural studies may be hampered by the fact that cannabinoids cause catalepsy and reduced motor activity in animals, but electrophysiological and neurochemical methods have proved their analgesic effects.

In pain conditions such as chronic constriction injury of the sciatic nerve, CB₁Rs were up-regulated within the ipsilateral dorsal horn of the spinal cord, supporting the involvement of the cannabinoid system in pain processing. The up-regulation of CB₁Rs leads to an enhancement of the effects of cannabinoid receptor agonists on hyperalgesia and allodynia after nerve injury [18].

In other experiments, the blockade of CB₁Rs induced hyperalgesia, suggesting a tonic activation of CB₁Rs by endocannabinoids [19, 20]. CB₁R agonists also exhibit direct effects on sensory nerve terminals, leading to an inhibition of the release of calcitonin gene-related peptide [21].

However, there are also important peripheral sites of cannabinoid analgesia. In several studies, local administration of cannabinoids into inflamed tissue attenuated hyperalgesia and allodynia via peripheral CB₁Rs, at doses that produced only minimal centrally mediated side effects [22, 23]. Activation of peripheral CB₁Rs could re-

duce mechanical activation of A- δ nociceptors from inflamed skin but not from non-inflamed skin [24] and attenuated hyperalgesia produced by thermal injury [25], nerve injury [26] and cancer [27, 28]. Moreover, the crucial role of peripheral cannabinoid receptors in the antihyperalgesic actions of systemically administered cannabinoids was also demonstrated by experiments with conditional peripheral CB₁R knockout mice. In these mice, the antihyperalgesic effects of systemically administered cannabinoids were nearly completely lost in models of carrageenan-induced inflammation and sciatic nerve injury-induced neuropathy [16].

In a vast number of studies, spinal, supraspinal and peripheral sites of cannabinoid analgesia could be identified.

Evidence that CB₂Rs play a role in analgesia was not present until 1998 [29]. Shortly thereafter, a CB₂R selective agonist was shown to have analgesic activity without typical cannabinoid CNS side effects [30]. CB₂R agonists did promote analgesia when injected peripherally, suggesting that CB₂Rs also modulate nociception [31, 32]. Since then, it has been shown that a number of different CB₂R agonists can modulate many types of pain, i.e. acute, inflammatory, neuropathic, post-surgical and cancer pain [33–44]. It is still not completely clear where these CB₂R agonists exert their analgesic activity. CB₂Rs were originally described as being restricted to cells of immune origin, but there is growing evidence for their expression in human primary sensory neurons, and increased levels of CB₂Rs in human peripheral nerves have been found after injury, particularly in painful neuromas. Several reports have suggested that the targets for these drugs are CB₂Rs expressed in the spinal cord pain pathway. In neuropathic pain models, both the up-regulation of spinal CB₂Rs and the efficacy of spinally administered cannabinoid CB₂R agonists could be demonstrated [39–41]. In contrast, the analgesic effect induced by the spinal administration of cannabinoid CB₂R agonists in inflammatory pain models seems to be limited, and study results are not completely consistent.

Analgesic effects of CB₂R agonists have been found in rats after the intraplantar administration of complete Freund's adjuvant (CFA), whereas no analgesic effect was found in the formalin test [39, 42]. In several experiments, spinal cannabinoid CB₂Rs were not up-regulated by different inflammatory processes such as CFA-induced paw inflammation [42] and CFA-induced arthritis [43] or acrolein-induced bladder inflammation in rats [44].

In some cases, CBR-mediated effects also involve the activation of the opioid system [40]. In addition, CBR ag-

onists enhance the effect of μ -opioid receptor agonists in a variety of models of analgesia, and combinations of cannabinoids and opioids may produce synergistic effects.

Clinical Studies on Pain: Cannabinoids and Acute Pain

Some trials have been performed to investigate cannabinoid-mediated analgesia by measuring pain thresholds in different controlled pain conditions in human volunteers using different cannabis preparations. In the first study [45], thermal and electrical pain thresholds were determined in healthy volunteers after a single dose of 20 mg of oral THC compared to placebo or 30 mg of morphine in a cross-over design. Surprisingly, after THC, lower pain thresholds were observed compared to morphine or placebo, pointing towards hyperalgesia. A second study, using two different human pain models, a circular sunburn and intradermal administration of capsaicin (the pungent constituent of chili peppers), was performed with orally administered THC-standardized cannabis extract compared to 5 mg of diazepam as an active placebo [46]. The pain thresholds were either unaltered (capsaicin) or significantly lower (sunburn) after administration of cannabis extract, also favouring hyperalgesia. In a third study, the effects of three different doses of smoked cannabis or placebo cigarettes were investigated in capsaicin-evoked pain. An analgesic effect was only seen after the medium-dose cannabis cigarette, whereas the lowest dose showed no analgesic effect at all and the highest dose again produced hyperalgesia [47].

In acute postoperative pain, orally administered cannabinoids had no analgesic effect at low doses of 5 mg of THC [48, 49]. Dose-dependent analgesia was found with higher doses of 10–15 mg of THC, but concurrently the intensity and frequency of side effects increased [49]. The recruitment of patients for the 15-mg THC group was stopped prematurely after a vasovagal syncope occurred in a young male individual.

The synthetic THC analogue nabilone produced significant hyperalgesia in a postoperative setting [50] in patients receiving the highest dose of 2 mg compared to 1 mg of nabilone, ketoprofen or placebo.

In contrast to the promising data from all animal studies, cannabinoids consistently showed no reliable or potent analgesic efficacy in acute pain in humans, and therefore they cannot be recommended for this condition.

Clinical Studies on Chronic Pain

Since in 2002 Marsicano et al. [51] were able to demonstrate in fear-conditioned rodents that the endogenous cannabinoid system plays a pivotal role in the extinction of adverse memories and pain conditioning, cannabinoids are supposed to have similar properties in chronic pain conditions in humans.

However, data from clinical trials are still not sufficient to give a clear answer in general. A recent meta-analysis investigating 18 randomized controlled trials on cannabinoids for the treatment of chronic pain [including studies of nociceptive, neuropathic and multiple sclerosis (MS)-related pain] suggests that the analgesic properties of cannabinoids are moderate, but their use may be partially or completely offset by potentially serious harms. Unfortunately, in this meta-analysis, the numbers needed to treat could not be calculated due to the designs of the included studies. Only NNHs were calculated, ranging from 5 (events altering motor function) to 8 (events altering cognitive function) [52].

Pain in MS

Most of the clinical trials with cannabinoids were performed in patients suffering from MS. Different types of pain can occur in these patients, and therefore both central neuropathic pain and spasticity-associated pain [53] in MS patients were investigated. Besides case reports and smaller studies, in one investigation, dronabinol was superior to paracetamol for the treatment of central pain in 24 MS patients [54]. In a second study, significant pain relief was seen in 66 MS patients using an oromucosal spray containing THC and cannabidiol (CBM) as an add-on medication [53]. The multicentre study by Zajicek et al. [55] also showed significant pain relief in MS patients with dronabinol or cannabis extract compared to placebo; however, this was not the main outcome parameter of the study. The main outcome parameter of this trial was spasticity, measured by means of the Ashworth Scale, an observer-based rating scale. No significant differences in the Ashworth Scale were found between the three groups, but patients performed better in functional tests under treatment with cannabinoids. From all those studies, there is an increasing amount of evidence to confirm anecdotal reports of symptomatic improvement in MS patients treated with cannabinoids, particularly with regard to muscle stiffness and spasticity, neuropathic pain, sleep and bladder disturbances. According to the results of the clinical trials, published guidelines as well as expert recommendations suggest cannabinoids as second-line

Table 1. Studies on neuropathic pain and cannabinoids

Study	Design	Indication	Cannabinoid	Efficacy	AEs and SEs
Maurer et al. (1990) [61]	RCT	spinal cord injury (pain, spasticity) (n = 1)	THC vs. codeine, vs. placebo p.o.	significant reduction of pain with THC and codeine, spasticity only with THC	none
Karst et al. (2003) [62]	RCT	neuropathic pain after trauma (n = 21)	ajulemic acid vs. placebo p.o.	significant pain reduction; NNT for 30% pain reduction between 2.14 and 5.29	tiredness, dry mouth 1 AE ¹
Berman et al. (2004) [58]	RCT	brachial plexus avulsion (n = 48)	CBM, oromucosal spray vs. placebo	significant pain reduction; NNT for 30% pain reduction 9; improvement of sleep	dizziness 1 AE ¹
Attal et al. (2004) [63]	open label	refractory chronic neuropathic pain, central and peripheral (n = 8)	THC p.o.	1 responder with significant pain reduction	AEs in 6 patients
Hagenbach et al. (2007) [64]	open label/RCT	spinal cord injury (n = 25)	THC p.o., rectal	significant reduction of spasticity, pain reduction in 4 patients	dry mouth, anxiety, tiredness
Nurmikko et al. (2007) [60]	RCT	peripheral neuropathic pain (n = 125)	CBM, oromucosal spray vs. placebo	significant reduction of pain and allodynia, improvement of sleep; NNT for 30% pain reduction 8.6	18% AE-related withdrawal in the CBM group
Abrams et al. (2007) [57]	RCT	HIV-associated neuropathy (n = 50)	cannabis cigarettes vs. placebo	significant pain reduction	mild SEs, sedation, dizziness, anxiety
Frank et al. (2008) [67]	RCT	neuropathic pain (n = 96)	nabilone vs. DHC p.o.	significant pain reduction with DHC	AEs with DHC and nabilone
Wilsey et al. (2008) [59]	RCT	central and peripheral neuropathic pain (n = 30)	cannabis cigarettes (2 different doses) vs. placebo	significant pain reduction	minimal SEs
Ellis et al. (2009) [56]	RCT	HIV-associated neuropathy	cannabis cigarettes vs. placebo	significant pain reduction; NNT for 30% pain reduction 3.6	sedation, dry mouth 2 AEs ¹
Selvarajah et al. (2010) [69]	RCT	diabetic PNP (n = 30)	CBM oromucosal vs. placebo	no difference	6 AEs ¹
Rintala et al. (2010) [70]	RCT	spinal cord injury (n = 7)	THC p.o. vs. placebo	no difference	dry mouth, fatigue, dizziness 1 AE ¹
Ware et al. (2010) [71]	RCT	neuropathic pain after trauma or surgery (n = 23)	cannabis, inhaled	significant pain reduction, improvement of sleep	dizziness, dry eyes, cough 1 AE ¹
Bestard and Toth (2011) [72]	open label	PNP (n = 101 for monotherapy and n = 119 for add-on)	nabilone vs. gabapentin	significant pain reduction (60%) in both groups for monotherapy and add-on	sedation in both groups, more withdrawals with gabapentin

RCT = Randomized double-blind placebo-controlled trial; PNP = Polyneuropathy; DHC = dihydrocodeine; NNT = number needed to treat; AE = adverse event; SE = side effect; p.o. = per os.

¹ Number of dropouts due to adverse events.

therapy for pain and spasticity in MS patients, because of the concern regarding the risk of abuse and psychiatric adverse events.

More trials are currently under way to investigate whether cannabinoids may have a longer-term role in reducing disability and progression in MS patients, because in rodent models of MS the progression of the disease was significantly slower in cannabis-treated animals.

Neuropathic Pain

Some studies have been performed in different chronic neuropathic pain conditions, e.g. cervical plexus avulsion, HIV-associated neuropathy or peripheral nerve lesions, using oral THC, CBM spray or smoked cannabis cigarettes compared to active or inactive placebo. In most of the studies, average pain relief of about 30% could be observed, which has to be regarded as merely moderate (table 1) [56–72]. Of special importance is the fact that the studies with smoked cannabis examining HIV neuropathy demonstrated a significant analgesic effect, because this type of pain has been notoriously resistant to other treatments recommended commonly for neuropathic pain.

Chronic Nociceptive Pain

The first clinical studies were already performed in 1975 by Noyes et al. [73, 74], who compared the analgesic effect of THC and codeine in cancer patients. They showed that the analgesic property of 10 and 20 mg of THC is approximately equivalent to 60 and 120 mg of codeine, respectively. However, higher doses of THC were more frequently associated with unwanted side effects such as sedation and drowsiness.

In recent years, studies with oral THC and nabilone as well as CBM were performed in patients suffering from rheumatoid arthritis, fibromyalgia syndrome (FMS) and cancer pain [75–82]. Compared to placebo, the patients in those studies experienced statistically significant pain relief that was again mainly around 30%.

However, besides the moderate pain relief, all studies consistently reported that cannabinoids improved mood, sleep and coping in the study subjects. FMS patients with clinically relevant depression seemed to have more benefit from cannabinoids than FMS patients without depression in one study.

One open-label clinical trial [83] reported synergistic analgesic effects of cannabinoids in combination with opioids and prevention of opioid tolerance [84]. Narang et al. [83] observed significant pain relief, reduced pain bothersomeness and increased satisfaction with the ther-

apy under add-on medication with dronabinol in patients suffering from chronic non-malignant pain. In one randomized, placebo-controlled study in patients with severe cancer-related pain, cannabinoids reduced pain in 43% of the patients with pain relief of between 30 and 50% when administered as an add-on medication [85].

Adverse Effects of Cannabinoids

In clinical trials, the therapeutic benefit of cannabinoids was often hampered by side effects leading to withdrawal of the therapy. The most frequent side effects are dizziness, drowsiness, sedation, dry mouth and cognitive impairment. Hypotension, hypothermia and tachycardia may also occur at the beginning of the treatment. Some individuals may experience anxiety or psychotic episodes under the influence of cannabinoids. These side effects are dose-related, occurring mainly after acute administration of high doses, and in most cases can be avoided by dose titration. However, patients with any history of psychosis, panic attacks or schizophrenia should not be treated with cannabinoids, since activation of these conditions by cannabinoids cannot be ruled out.

Long-term heavy cannabis use may also lead to cognitive impairment and compromised memory, although in humans, no ultrastructural changes were found post-mortem in the brain of cannabis users [86].

Acute administration of cannabinoids can cause marked tachycardia and hypotension. Cardiac output may be increased, with a consecutive increase in cardiac oxygen consumption and cardiac work. Smoking marijuana seems to be particularly hazardous, since due to the deep inhalation techniques of experienced cannabis smokers, 5-fold higher carboxy haemoglobin levels may be achieved than in tobacco smokers.

Some case reports suggest that marijuana smoking may increase the acute risk of myocardial infarction, stroke, conduction abnormalities and arrhythmias [87–89]. Interestingly, to date, cardiovascular events were reported exclusively after smoking cannabis, not after oral or submucosal administration of any medical cannabinoid preparation. Despite the lack of such reports and for safety reasons, cannabinoids should not be prescribed to patients with coronary heart disease or a history of other cardiovascular events.

Since most side effects occurred after acute administration of high cannabinoid doses, individual dose titration is necessary to reduce the frequency and intensity of unpleasant side effects, especially in elderly persons.

Conclusion

The discrepancy between the clinical results and the animal experiments (mainly performed in rodents) may be in part due to species-related differences, since humans are supposed to be less sensitive to cannabinoids. However, one should be aware that it is impossible to translate the results of experiments with young male inbred rats directly into a clinical situation, where the majority of chronic pain patients is female and middle-aged. All the standardized and well-defined animal experiments like chronic constriction injury of the sciatic nerve or the injection of CFA do not mirror any real clinical pain condition and can show us only one small part of the neurobiological pain mechanisms that may be relevant in a patient.

So, compared to the promising results from animal experiments, the clinical data are far less clear. In acute pain, a kind of dose-dependent, bi-phasic effect of cannabinoids was observed, making the prediction of their analgesic effect in clinical settings difficult. Since acute administration of higher doses of cannabinoids was consistently associated with a higher risk of severe adverse events like acute psychosis, anxiety and hypotension, cannabinoids cannot be recommended for the treatment of acute pain.

The pain relief in patients suffering from chronic pain was hardly more than 30% in most of the clinical trials. Although the pain relief was statistically significant, from a clinical point of view it must be considered as only moderate. Nevertheless, a 30% improvement in pain scores is regarded as meaningful by the guideline on clinical medical products intended for the treatment of neuropathic pain of the European Medicines Agency.

However, it must be mentioned that cannabinoids showed significant pain relief mainly in placebo-controlled trials, whereas in head-to-head comparisons they did not show a clear superiority over 'weak' opioids or other therapeutics. The conclusions that can be drawn from many of the cited studies are limited due to small sample sizes, short duration of the trials, unclear adequacy of blinding and unequal 'cannabis experience' of the participants.

Currently, according to the number of investigations and their results, the best indication for cannabinoids seems to be MS-related pain. In Canada and an increasing number of European countries, cannabinoid medications are already approved for this indication. Data showed that a daily dose of approximately 10–15 mg of THC is necessary for pain relief, a dose with which side

effects frequently occur. Therefore, cannabinoids are only assessed as a second-line therapy in some published guidelines and expert recommendations.

The efficacy of cannabinoids for other chronic pain syndromes remains less clear. They may be helpful adjuvants in painful conditions like HIV-associated neuropathy, spinal cord injury, endometriosis, cancer, fibromyalgia, inflammatory bowel diseases and other chronic pain conditions, not only because of their analgesic properties.

Besides relieving pain, cannabinoids have shown other beneficial effects like improvement of mood, sleep and quality-of-life scores in study subjects. The improvement of sleep and sleep quality is an important aspect, since sleep disturbances may contribute to greater pain, disease activity and mood disturbance in chronic pain patients and increase their degree of disability. Cannabinoids have also been approved against emesis in cancer patients undergoing chemotherapy and against HIV-associated cachexia since 1987.

To conclude, cannabinoids are analgesics, but their analgesic properties are merely moderate to mild, insufficient for the treatment of severe pain, and their analgesic effects are less predictable. However, cannabinoids are different from classical analgesics like non-steroidal anti-inflammatory drugs or opioids, since they exert a variety of other effects that may be useful for an individual patient. Therefore, cannabinoids are useful as co-analgesics or even as an adjuvant with a unique pharmacological profile within a multimodal therapeutic concept for special groups of patients or some individuals.

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