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The Analgesic Potential of Cannabinoids

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Abstract

Historically and anecdotally cannabinoids have been used as analgesic agents. In recent years, there has been an escalating interest in developing cannabis-derived medications to treat severe pain. This review provides an overview of the history of cannabis use in medicine, cannabinoid signaling pathways, and current data from preclinical as well as clinical studies on using cannabinoids as potential analgesic agents. Clinical and experimental studies show that cannabis-derived compounds act as anti-emetic, appetite modulating and analgesic agents. However, the efficacy of individual products is variable and dependent upon the route of administration. Since opioids are the only therapy for severe pain, analgesic ability of cannabinoids may provide a much-needed alternative to opioids. Moreover, cannabinoids act synergistically with opioids and act as opioid sparing agents, allowing lower doses and fewer side effects from chronic opioid therapy. Thus, rational use of cannabis based medications deserves serious consideration to alleviate the suffering of patients due to severe pain.

Keywords

pain; cannabinoid; opioid; marijuana; cannabis; HIV/AIDS; cancer

Introduction

Cannabinoids are derivatives of Cannabis sativa, the hemp plant, which evolved in the temperate regions of Central Asia. The female plants produce a fragrant amber-colored resin that contains cannabinoids. Crushed cannabis seeds were used as food in Asia in the past, especially during famines, and continue to be used as baby food in sub-Saharan Africa. Cannabis continues to be incorporated into a variety of recipes, ranging from *bhang* (a recreational drink) in India, chocolates and dates in the Middle-East, and curries in Thailand. The distinguishing feature of cannabis is the psychoactivity of its derivatives. There are at least 60 active compounds than can be extracted from cannabis [1]: Δ9-tetrahydrocannabinol (Δ9-THC) being the main one; others include cannabidiol (CBD), cannabinol (CBN), tetrahydrocannabivarin (THCV), cannabichromene (CBC), etc. These compounds are responsible for the psycho-activity of cannabis products such as hashish, marijuana and hashish oil. The THC content of these varies from 5% in marijuana to 80 % in hashish oil [2].

Cannabis was used as a medicine in ancient China (2700 BC) and India (1000 BC)[1, 3]. It was brought to Europe by Scythian invaders from Central Asia, entered Western medicine in

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early and middle 19th century and was widely used for its medicinal properties [3]. Cannabis extract and medications were marketed by pharmaceutical companies over-the-counter in the United States in late 19th to early 20th century. The accompanying increase in recreational marijuana smoking led to formation of the Marijuana Tax Act in 1937. Eventually, cannabis was omitted from the National Formulary and Pharmacopoeia. In the 1960s, the recreational use of cannabis peaked, followed by a renewal of scientific interest in the plant for its medicinal properties [4]. Since then cannabinoids have been studied or used in a multitude of applications, many of which relate to their potential use as analgesic agents.

Currently, opioids are the only analgesics for treating severe pain. However, in some patients, they are associated with rather unpleasant side effects, including sedation, loss of appetite, initial nausea, persistent constipation [5] and respiratory depression [6]. Moreover, issues such as tolerance, dependence and opioid induced hyperalgesia remain a major deterrent in opioid use [7]. In view of these side- effects and the decrease in analgesic efficacy over time [8], there is a need to explore alternative or adjunct medications to opioids in management of severe pain; and cannabinoids are being currently explored as one possible alternative. This review discusses the current and potential medicinal use of cannabinoids, especially for pain management, and considers whether they should be explored as a feasible adjunct or alternative to opioids, based on current data from experimental and clinical studies.

Classification of cannabinoids

Based on their origin, cannabinoids are classified into 3 categories: phytocannabinoids (plant origin), endocannabinoids (present endogenously in human or animal tissues) and synthetic cannabinoids. Tables 1, 2 and 3 list the common cannabinoids and their receptors with which they interact on the cell surface.

Cannabinoid receptors and signaling pathways

Cannabinoids mainly act via 2 different receptors: (i) the cannabinoid-1 (CB-1) receptor, predominantly expressed on the neurons; and (ii) the cannabinoid-2 (CB-2) receptor, predominantly expressed on cells of the immune system [9]. However CB-2 receptor expression is seen on glial as well as neuronal cells in several areas of the brain [10]. In the neurons, CB-1 receptors are preferentially located in the presynaptic areas and are seen more often on the inhibitory neurons than the excitatory ones [11]. The pattern of distribution suggests that the psychotropic effects are mediated mainly via the CB-1 receptors. CB-1 receptors are present in high levels in hippocampus (particularly in the dentate molecular layer and the CA3 region), lateral part of the striatum, globus pallidus, entopeduncular nucleus, substantia nigra pars reticulata, and cerebellar molecular layer. The thalamus and the brainstem are characterized by low levels of CB-1 receptor expression, which is consistent with the non-lethality of cannabinoids. In the spinal cord, moderate expression in seen in the dorsal horn [10].

Cannabinoid receptors are 7-transmembrane G-protein coupled receptors (GPCR) [12]. Ligand binding to CB-1 receptors results in inhibition of adenylyl cyclase and the voltage activated calcium (Ca^{2+}) channels. Activation of CB-1 receptors thus decreases cAMP production and Ca^{2+} conductance, while increasing potassium conductance and the activity of mitogen-activated protein kinases (MAPK). Binding of cannabinoids to CB-1 receptors is critical to their antinociceptive activity. CB-1 receptor activation suppresses the nociceptive sensitization by influencing the release of neurotransmitters including acetylcholine, norepinephrine, gamma-amino butyric acid (GABA), glycine, dopamine, serotonin and cholecystokinin (CCK) from the presynaptic terminal, possibly through blunting of

membrane depolarization and exocytosis via modification of the calcium and potassium channels [11], [13]. The modulation of intracellular calcium levels by CBD in neuronal cells appears to occur by using the mitochondria as a reservoir [14]. CB-2 receptor activation also inhibits adenylyl cyclase, but does not influence ion conductance [15]. Cannabinoids are suggested to bind some other types of receptors as well [16]. The transient receptor potential vanillloid 1 (TRPV1) receptor is present on sensory neurons and responds to nociceptive stimuli, however it is also present in the brain where it binds anandamide [17]. GPR 55 is an orphan G protein coupled receptor that is currently being explored as a cannabinoid receptor. It binds Δ9-THC, CP-55940, and endocannabinoids including anandamide [11] The 5HT-3 and NMDA receptors have also been implicated in cannabinoid signaling [11].

Cannabinoids modulate both the cell proliferation as well as cell survival pathways, albeit sometimes effects may be opposite depending on the cell type (Figure 1). Cannabinoids regulate the cell cycle via their effects on different members of the MAPK family, and PI3k/Akt pathways [18], [19] in neurons. On the contrary, cannabinoids also promote apoptosis through activation of JNK [20] and inhibition of ERK and PI3k/Akt [21], [22] pathways in cancer cells. Other studies also show a selective inhibitory effect of cannabinoids on cancer cells, while sparing normal cells [23],[24]. Cannabinoids influence sphingolipid-metabolizing pathways to induce sphingomyelin breakdown and generate ceramide [13]. The increased ceramide [25] via inhibition of PI3k inhibits PKB/Akt and ERK pathways, resulting in apoptosis [22]. THC also causes p8 upregulation via ceramide; p8 is a transcription factor with a regulatory role in the apoptotic cascade [26]. However, CB-2 antagonist rimonabant induces G1/S arrest and inhibits cell proliferation in breast cancer cells, though apoptosis or necrosis is not observed [27]. CB-2 agonist JWH-015 inhibits cisplatin-induced apoptosis in auditory cell lines [28]. Hence cannabinoids appear to have complex effects on the cell-cycle, which have not yet been completely defined. However, it appears that the cannabinoid signaling is cell-specific and may also be dependent upon specific agonists used. Importantly, this variability in cell signaling induced by cannabinoids in neuronal and non-neuronal cells suggests that the effect of cannabinoids will need to be examined for both their anti-nociceptive activity and the peripheral effect for individual pathological condition.

Routes of cannabinoid use

Smoking and oral ingestion are the common routes of cannabinoid use. Smoking results in rapid absorption and onset of psychoactive effects, and is the preferred mode of recreational use. Marijuana use is followed by a disruption of short-term memory, cognitive impairment, a sense of slowing of time, mood alterations, enhanced body awareness, reduced ability to focus, incoordination, and sleepiness [9]. Ingestion of hashish leads to delayed onset and longer duration of actions. THC can also be inhaled in a vaporized form without smoking, that avoids the inhalation of combustion by-products, while providing higher bioavailability. [2] When Δ9-THC enters the bloodstream, it is metabolized to 11-hydroxy Δ9-THC, which is absorbed into the adipose tissue, where it stays for 30 minutes before being released back into circulation and reaching the brain. [2]. In animal studies, both intraperitoneal and localized administration of cannabinoids have been used [29][30][31][32], [33]

Cannabinoids for analgesia – animal studies

a) Neuropathic pain

Cannabinoids have been studied in various types of neuropathic pain including nerve injury, chemotherapy-induced, diabetic neuropathy, etc. CB-1 receptors have been found to be upregulated in the thalamus [34] and the spinal cord [35] after nerve injury in rat models of neuropathic pain. Another study showed CB-2 receptors were induced in a localized area of

spinal cord consistent with the location of nerve injury [36]. Systemic administration of both WIN-55,212-2 and HU-210 suppressed mechanical allodynia and thermal hyperalgesia in a rat model of trigeminal neuralgia [37]. WIN-55,212-2 also provided antinociception in a model of sciatic nerve injury, with enhanced action if administered pre-emptively [38]. Intrathecal JWH-133, a CB-2 agonist, also significantly improved mechanical allodynia after sciatic nerve injury [39]. Mechanical allodynia developing in diabetic rats also responds to WIN-55212-2 administration [40], as does thermal hyperalgesia and tactile allodynia induced in rats by the chemotherapeutic agent paclitaxel [41]. Mechanical allodynia induced by vincristine [42] and cisplatin [43] administration in rats is suppressed through both CB-1 and CB-2 receptor agonism. Pure CB-2 agonists also decrease chemotherapy induced neuropathic pain [44]. Furthermore, synergistic anti-nociceptive action between Δ9-THC, CBD and other extracts from cannabis in neuropathic pain has been suggested [45]. These studies demonstrate that cannabinoids can be potentially used as analgesics in treating neuropathic pain accompanying diverse pathologies.

b) Inflammatory pain

Both CB1 and CB2 receptors are involved in the mediation of inflammatory pain [46]. WIN-55,212-2 has been shown to attenuate the delayed phase of oro-facial pain induced by formalin injection in rats [47]. The action of WIN-55,212-2 in inflammatory pain appears to be mediated via both CB-1 and CB-2 receptors [48]. Systemic HU-308, a novel CB-2 agonist also attenuated inflammatory pain during hot plate test in mice [49]. Inflammatory pain and swelling in mouse hindpaw were relieved by systemic administration of both non-selective HU-210 and CB-2 selective JWH-133 [31], and also by local injection of CB-2 agonist AM1241 [32], [33]. Since, inflammatory pain is a hallmark of several chronic diseases including sickle cell disease and cancer, cannabinoids appear to be a promising therapy to treat severe pain in these diseases.

c) Cancer pain

Both endogenous and exogenous cannabinoids are being investigated for a role in cancer pain management. Cannabinoids have been found effective in increasing the threshold at which pain is perceived in tumor-afflicted mice [50]. Mechanical hyperalgesia in a murine model of bone cancer pain is associated with decreased anandamide levels in the affected area and was alleviated by local injection of anandamide. Hyperalgesia in this model was tested by measuring the paw withdrawal frequency in mice injected with fibrosarcoma cells into the calcaneum [29]. The cannabinoid agonist WIN-55,212-2 has also been shown to attenuate tumor induced hyeralgesia in mice, through peripheral action on CB-1 and CB-2 receptors, rather than by central action [51], [50]. Another study suggested that the antinociceptive action of WIN-55,212-2 in a mouse tumor model is solely via CB-1 receptors [48]. Systemic administration of CP-55,940 also attenuates tumor-induced hyperalgesia [30]. These studies suggest that different cannabinoids may offer pain relief in cancer by both systemic and peripheral routes, primarily via CB-1 receptors, and the route of administration may be tailored to the specific need.

The preclinical studies described above provide a rationale for further evaluation of cannabinoid receptor agonists in different types of pain. Both CB-1 and CB-2 receptors appear to be involved in pain modulation, and selective agonists may be useful when the specific role of each receptor is fully characterized in each type of pain. Especially in cases of pain attributable wholly or partly to inflammation, it may be worthwhile to explore a local route of administering the cannabinoid and thus avoid systemic side effects.

Synergism with opioids

a) Experimental studies

Opioids and cannabinoids both provide antinociception through G-protein coupled mechanisms, and many studies have explored synergistic interactions between them. A study using subcutaneous morphine and intraperitoneal THC in rats showed equivalent antinociception using high dose morphine or high dose THC or a low dose combination of both. In addition, the combination was shown to circumvent the development of tolerance when compared to either drug alone [52]. Pretreatment with HU-210 also increased the antinociceptive effect of morphine injected into the periaqueductal gray and prevented the development of tolerance [53]. Synergistic effect with an opioid-cannabinoid combination has been shown in other studies as well, using systemic [54, 55, 52, 56, 57] or topical agonists [58]. THC also enhances the analgesic action of fentanyl and buprenorphine patches [59]. However, ultra-low dose naltrexone has also been shown to enhance the anti-nociceptive action of WIN 55,212-2, while high dose naltrexone does not [60]. This is similar to enhancement of the antinociceptive action of morphine by ultra-low concentrations of naloxone or naltrexone [61], [62]. Δ9-THC (both by itself and in combination with morphine) has been shown to provide better anti-nociception in diabetic mice than in non-diabetic arthritic mice, and this has been correlated to the lower endogenous opioid levels in diabetic mice [63]. CB-2 receptor activation by AM1241 causes the release of β-endorphin from keratinocytes, and the antinociceptive effect of AM1241 in rats is blocked by antagonism of the μ opiod receptor and by antiserum to β-endorphin [64]. Also, CB1 receptor knockout mice appear to have lesser opioid addiction and withdrawal [65], suggesting a role for cannabinoid receptors in opioid signaling pathways. Conversely, cannabinoid withdrawal symptoms were decreased in double μ and κ opioid receptor knockout mice [66], suggesting a relationship between opioid and cannabinoid receptor activities. These data support the harmonious and even supportive use of cannabinoids in conjunction with opioids. Clinical studies below support the experimental data on combined and/or simultaneous use of opioids and cannabinoids to treat pain.

b) Clinical studies

Most studies evaluating synergism between opioids and cannabinoids have been in healthy subjects, and the subject needs to be studied further in specific disease models. A double-blind randomized controlled trial evaluating 30 mg morphine or 20 mg Δ9-THC or a combination of both in experimental pain conditions in healthy human volunteers suggested a hyperalgesic effect of Δ9-THC when used alone, that disappeared when used with morphine [67]. A slightly additive analgesic action was observed with the THC-morphine combination when testing sensitivity to electric stimulation [67]. However, no synergism was noted in a randomized double blind study using adjuvant Δ9-THC in the acute post-operative pain in post prostatectomy patients on patient-controlled analgesia with opioid agonist piritramide [68].

Thus, adjunct use of cannabinoids may permit the use of lower doses of opioids than otherwise required, thus acting as an opioid sparing agent in similar situations. However, in other conditions, the addition of a cannabinoid may confer no additional benefit, so the optimal therapy for pain management in specific conditions remains an area for future research. Table 4 compares certain features of cannabinoids and opioids relevant to their use as antinociceptive agents.

Cannabinoid as an Anti-emetic and Appetite stimulant

Currently dronabinol (synthetic Δ9-THC) and nabilone are approved for treatment of chemotherapy induced nausea and vomiting (CINV) [87]. From the patients' perspective,

nausea and vomiting is perhaps the most distressing effect of chemotherapy. While 5HT-3 receptor antagonists are effective for acute onset nausea and vomiting, they are not so beneficial in delayed nausea and vomiting. A recent systematic review concluded that nabilone is superior to placebo, domperidone and prochlorperazine in the management of CINV, but not superior to metoclopramide and chlorpromazine [88]. Oral dronabinol combined with prochlorperazine has been shown to be more effective than either agent alone in controlling CINV [89]. While many studies have shown dronabinol to improve mood, appetite and to decrease nausea in patients with AIDS or advanced cancer [90], a recent study comparing cannabis extracts (CE), Δ9-THC and placebo in patients with cancer related anorexia cachexia syndrome found no significant advantage of CE or Δ9-THC over placebo with regard to appetite, quality of life or toxicity [91].

Cannabinoids in HIV/AIDS

Many HIV infected patients smoke marijuana for a variety of reasons, including symptom relief and reducing symptom frequency; the users report improvement in appetite (97%), muscle pain (94%), nausea (93%), anxiety (93%), nerve pain (90%), depression (86%), and paraesthesia (85%). However, many cannabis users (47%) also reported associated memory deterioration. [92]. Smoked marijuana appears to have a beneficial role in reducing neuropathic pain in HIV, and the studies discussing this are detailed below. In a subanalysis of data from a multicountry randomized clinical trial studying self-care symptom management in HIV patients, anxiety was found to be lower in marijuana users than nonusers. Marijuana offered slightly better overall relief then the prescription/OTC medications for a number of symptoms (including anxiety, depression, nausea, vomiting, diarrhea, neuropathy). Marijuana users reported better overall medication effectiveness than non-users, however it is unclear whether it is attributable to the euphoric effect of marijuana or a real synergism with the medications [93]. Thus, cannabinoids may have multiple therapeutic functions in both, the central nervous system and peripheral organ disease.

Cannabinoids In Multiple sclerosis

Many randomized clinical trials with cannabinoid medications have been conducted in multiple sclerosis (MS). Patients with multiple sclerosis have diverse types of pain: dysesthesias, back pain, muscle pain, etc; and each type of pain needs to be managed differently [94]. Cannabinoids have a role in relieving pain, spasticity, tremor, nocturia and improving general well being in MS (Table 5). The non-psychotropic cannabinnoid HU-211 has been shown to decrease clinical signs and improve survival in rats with MS [90]. Cannabinoids, especially endocannabinoids and CB-2 agonists are postulated to protect against neuro-inflammation, and may thus be beneficial for management of MS [90]. A randomized controlled trial with 667 MS patients using oral Δ9-THC or a cannabis extract Cannador®; found subjective improvement in subjects' self-reported sense of spasticity and pain, but no objective improvement in spasticity [95] by the Ashworth scale, [96]. No difference was noted between Δ9-THC and Cannador®[95]. Sativex® is an oromucosal spray containing Δ9-THC (27 mg/mL) and cannabidiol (CBD)(25 mg/mL), with a dosage of 100 μL/spray [97]. It was found to decrease mean pain intensity and reduce sleep disturbance in MS [98]. A 2 yr open label study as a follow up of this trial using Sativex® in 63 MS patients showed it to be effective in decreasing pain, however less than half of the subjects completed the trial [99]. Oral dronabinol achieved a modest reduction in pain intensity in MS and related conditions [100]. However, another study found no benefit from either Δ9 THC or a cannabis extract containing both THC and CBD [101]. Yet, a metanalysis of cannabis based medications in MS and other types of neuropathic pain concluded that cannabinoids were superior to placebo [102]. All these studies found dizziness to be the most common adverse effect, and that the incidence was higher in the

treatment groups. Overall, cannabinoids appear to be effective in treating pain in MS, and would need to be further evaluated for their optimum use in MS.

Clinical studies with cannabinoids in pain

The trials focusing on MS and related etiologies have already been discussed above. The text below focuses on clinical studies using cannabinoids in other conditions associated with pain. Further details of these studies and other clinical trials using cannabinoids are discussed in Tables 6 & 7. Studies using smoked cannabis in HIV associated sensory neuropathy and other types of neuropathic pain have found that it offers clinically significant analgesia to a large number of subjects [112], [114, 115] but often with associated neurocognitive and psychoactive effects, especially at higher doses [115]. Improvement was noted in pain, mood and daily functioning [112], but not in evoked pain [115]. Sativex® was found to offer significant pain relief, as well as improvement in sleep and allodynia in neuropathic pain of various etiologies [116]. A randomized, double-blind, placebo-controlled crossover trial of different cannabis based medicinal extracts (THC only, CBD only, THC + CBD) was undertaken on a set of 34 patients with chronic pain (mainly neuropathic) uncontrolled by their usual medications. It showed improvement in control of pain and an improved quality of sleep in all, while the psychoactive effects were noted to be manageable [118]. Sativex® and a THC predominant cannabis extract GW-2000-02 both offered significant analgesia in subjects with neuropathic pain from brachial plexus avulsion [113]. However, a study comparing escalating daily doses of nabilone (maximum 2 mg) and dihydrocodeine (maximum 240mg) in patients with severe neuropathic pain found dihydrocodeine to offer clinically significant pain relief to more patients than nabilone; interestingly, no subject responded to both agents [117]. In cancer patients, nabilone provided multi-symptom relief, including pain relief, as compared to patients who did not receive nabilone [106]. As an adjuvant drug added to opioids, it also improved pain control and the quality of sleep in patients with chronic non-cancer pain [107]. A systematic review in 2001 of all randomized controlled trials done with cannabinoids in various types of pain concluded that in cancer pain, cannabinoids were of the same efficacy of codeine, while being associated with dose limiting CNS depressant effects [119]. A recent review of the clinical trials conducted with Sativex® and other cannabis extracts in various types of pain observed a benefit in a range of conditions, including MS, cancer, irritative urinary symptoms, neuropathy, peripheral nerve injury and spinal cord injury. The only condition where benefit was not noted was post-herpetic neuralgia [97]. Δ9-THC has analgesic and other beneficial effects in fibromyalgia and rheumatoid arthritis as well [110], [111]. Interestingly, studies in healthy human volunteers using oral cannabis extracts in acute pain models do not show any analgesic effect, but rather suggest a hyperalgesic action [85]. Studies regarding the use of cannabinoids for post-operative analgesia suggest that while cannabis extract Cannador® might potentially be beneficial [108], Δ9-THC offers no benefit and may actually provoke hyperalgesia [84], [109]. Therefore, different cannabis-derived drugs appear to have differences in effectiveness in treating pain and/other symptoms in a variety of diseases. The effort needs to be targeted to identify disease and symptom-specific therapeutic potential of specific cannabis-derived drugs.

Can Cannabinoids be useful in Sickle cell disease?

We did not find any studies evaluating cannabinoids as analgesic agents in sickle cell disease (SCD). However, a questionnaire-based study evaluating the prevalence and reasons for marijuana use in SCD patients found that 31 of the 84 respondents reported cannabis use. While cannabis use was not found to vary with the severity of the disease, 52% of the users said they used it to reduce or prevent acute or chronic pain; other reasons were to improve sleep, mood or to aid relaxation [120]. Pain in SCD is a result of vascular occlusion, tissue

infarction and inflammation [121], and is widely prevalent and often undertreated [122]. Currently used analgesics in SCD include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, ketorolac, corticosteroids, tramadol and adjuvant agents. SCD patients with chronic pain are generally treated with a long acting opioid with addition of short acting opioids for breakthrough pain [121] Patients being treated with opiods for acute pain often suffer from nausea and vomiting [123]. Cannabinoids are commonly used to control nausea and vomiting in other settings, and could be potentially beneficial in this scenario as well. Cannabinoids, endocannabinoids and non-cannabinoid derivatives of the cannabis plant have also been found to have anti-inflammatory properties [124], which may be helpful in SCD. Transgenic sickle mice have been found to be markedly sensitive to ischemia-reperfusion injury [125]. CB-2 receptor activation by JWH-133 has been found to protect from cardiac ischemia reperfusion injury [126], [127] and may help in SCD as well. CB-2 receptor activation and CB-1 receptor inhibition has beneficial effects in cerebral ischemia [128], [129]. Vasocclusion being the pathology behind the pain in SCD, these factors should be considered when evaluating the role of cannabinoids as analgesics in this condition. Since SCD is a condition where the patient suffers severe acute episodes superimposed on a background of chronic lifelong pain, newer modalities need to be investigated to help achieve a better quality of life. Cannabinoids could possibly be used as adjunct agents along with opioids to decrease opioid dose and achieve better pain control. They also possess the potential to favorably modify the disease process via various mechanisms of central and peripheral activity discussed above.

Side effects of cannabinoids

Epidemiological studies have reached diverse conclusions regarding the association of cannabis with various cancers. A case-control study showed no increase in risk of head and neck cancer with cannabis use [130]. Some studies show higher lung cancer rates in marijuana smokers [131], [132], while some do not find any such association [133]. Maternal marijuana use, especially in the first trimester, is associated with an increased risk of neuroblastoma in the child [134]. Marijuana smoke has been shown to be mutagenic [135, 136], while THC by itself is not mutagenic [137, 138]. Equivocal proof of carcinogenicity of THC in B6C3F1 mice was found by one study [139]. These mice when treated with THC for 2 years showed an increased incidence of thyroid follicular cell adenoma [139, 140]. In contrast, THC was found to increase apoptosis and improve survival in murine cancer models and in human lymphoma and leukemia [141]. Moreover, the cannabinoid HU-331 is anti-angiogenic in vivo and vitro, suggestive of an inhibitory effect on cancer progression [142]. It appears that cannabinoids may have two opposite effects on cancer: tumor regression via promotion of apoptosis, and tumor promotion via suppression of immunogenicity [13]. Δ9-THC has been shown to inhibit angiogenesis and cell cycle progression in tumor cell lines, especially in glioma cells [143, 83]. WIN-55,212-2 and other cannabinoid agonists have been suggested as potential therapeutic options in prostate cancer [144]. It appears that past conflicting epidemiological data regarding association of marijuana smoking and cancer may not necessarily apply to Δ9–THC and other cannabis derivatives during therapeutic use via a non-inhalational route; however, caution may still be exercised while awaiting conclusive data.

Cannabinoids obviously have a potential to be misused and carry the risk of addiction. Prior psychiatric evaluation before prescribing cannabinoids has been suggested as one way to decrease this risk. Cannabis use in adolescence and young adulthood may have lasting effects on the brain and behavior [145]. Marijuana smoking has been postulated to contribute to the development of schizophreniform disorders [146], besides the risk of brief psychotic features with acute use [147], especially in the adolescent population. Diminished cognitive function in adolescent cannabis users [148] is also an area of concern. Chronic

cannabis users are also at risk of developing the amotivational syndrome, characterized by apathy, lack of activity, incoherence, blunting of cognition and affect [90]. However, all this data is from marijuana users, and not from a controlled therapeutic use of cannabinoids. It cannot be said for certain that long-term therapeutic use of cannabinoids will show the same risks. An 8 week study of cognition in patients with multiple sclerosis on Sativex® did not show any worsening of cognition, however it did suggest that at higher doses, psychopathological problems may occur [149]. Some preclinical studies also show development of tolerance to various actions of cannabinoids [150], including antinociception [151]. Recreational cannabis use is associated with a withdrawal syndrome consisting of tiredness, yawning, depression, anxiety, psychomotor retardation, reported at a prevalence of 57.7 % among frequent cannabis users [152]. Cannabinoids have been reported to cause motor impairment in the form of cerebellar incoordination [153], and the pathway appears similar to that of ethanol induced incoordination [154]. These concerns may need to be addressed while exploring the therapeutic use of cannabinoids.

Conclusion

Management of severe chronic pain is best done by a multi-pronged approach, individualizing it not just according to the disease but also according to patient preferences and their side effect profiles. Currently there is intriguing evidence from animal studies showing efficacy of cannabinoids as antinociceptive agents, however data from human studies is still emerging. Cannabinoids may form a useful adjunct to current analgesic drugs in many conditions, especially in low doses incapable of inducing hyperalgesia or other side effects. They can also be used as rescue drugs when opioid analgesia is ineffective or inadequate, or as opioid sparing agent. They also appear to antagonize several side effects of opioids, and the opioid-cannabinoid combination may become a very useful agent in the long-term management of severe pain. Preclinical data also suggest a beneficial effect of cannabinoids on the disease process in HIV, cancer, and MS. While smoked marijuana tends to be a controversial territory, evidence points to significant multi-symptom relief from it especially in HIV patients. Cannabis derived medications deserve to be investigated in rigorously designed studies so that their role in managing severe and chronic pain in various conditions can be more clearly defined. The legalization of medical marijuana would also enable more clinical trials in humans, and development of cannabis-derived drugs for multiple disease processes, in addition to treating severe pain. Moreover, examination of cannabinoids and their receptors may potentially lead to a new understanding of disease processes as well. Thus, the medical, as well as the general community, need to move beyond preconceived notions about cannabis, and focus on its potential advantages in treating a host of conditions, including severe pain.

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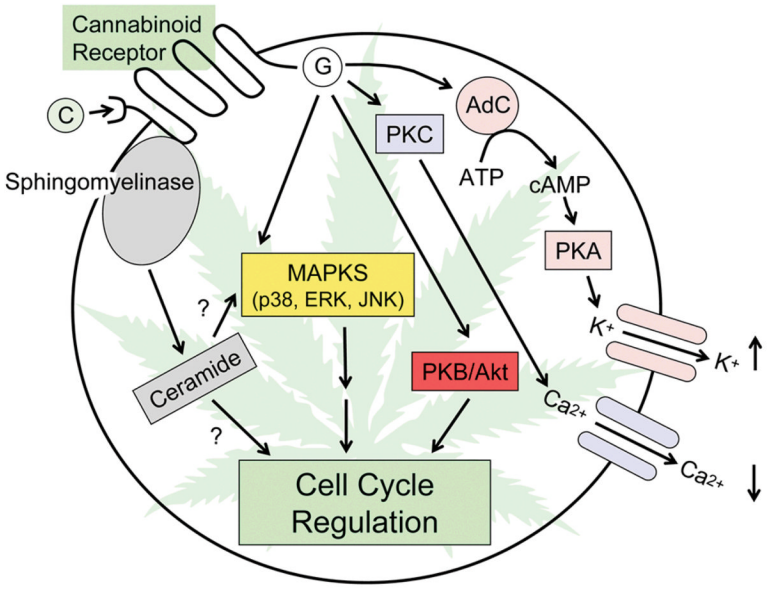

Figure 1.

Cannabinoid receptor signaling leads to cell cycle regulation and potassium and calcium conductance. CB-1 receptor activation modifies the activity of calcium and potassium channels and the activity of intracellular protein kinases. Cannabinoids also induce generation of ceramide, which affects the cell cycle via protein kinases and other mechanisms. C=Cannabinoid receptor agonist; G= G protein; AdC=Adenylyl cyclase; PKA= Protein kinase A; PKC= Protein kinase C; PKB= Protein kinase B= Akt; MAPK=Mitogen-activated protein kinase; ERK= extracellular signal-regulated kinase; JNK= c-Jun N-terminal kinase.

Table 1

Phytocannabinoids*

Substance	Receptors
Δ9-tetrahydrocannabinol(Δ9-THC)	CB-1,CB-2
Cannabinol	CB-1,CB-2
Cannabinol	CB-2>CB-1
Tetrahydrocannabivarin	CB-1 & CB-2 antagonist

*All substances are agonists at the mentioned receptors unless specified otherwise.

CB-1: Cannabinoid-1 receptor

CB-2: Cannabinoid-2 receptor

Table 2

Endocannabinoids*

Substance	Receptors
Anandamide (AEA)	CB-1, CB-2, TRPV-1
2-Arachidonyl glycerol (2-AG)	CB-1
2-Arachidonyl glyceryl ether	CB-1, CB-2
N-Arachidonyl dopamine (NADA)	CB-1

* All substances are agonists at the mentioned receptors unless specified otherwise.

CB-1: Cannabinoid-1 receptor

CB-2: Cannabinoid-2 receptor

Table 3

Synthetic Cannabinoids*

Substance	Receptors
Dronabinol (synthetic Δ9-THC)	CB-1, CB-2
Nabilone (Δ9-THC analogue)	CB-1,CB-2
CP-55940	CB-1, CB-2
WIN-55,212-2	CB-1
HU-210	CB-1,CB-2
HU-211	None
JWH-133	CB-2

*All substances are agonists at the mentioned receptors unless specified otherwise.

CB-1: Cannabinoid-1 receptor

CB-2: Cannabinoid-2 receptor

Table 4

A comparision of opioids and cannabinoids in pain management

Opioid	Cannabinoid
High dose opioids promote myoclonus and seizure activity through μ and κ receptors [69]	Endocannabinoids and CB1 agonists appear to have anticonvulsant activity [70], [71], [72]
Nausea, vomiting and constipation are common during opioid therapy [73]	Cannabinoids are used as anti-emetic, especially in chemotherapy induced nausea and vomiting [74]; In cases of chronic cannabis abuse, hyperemesis has been reported [75]; Constipation seen as a mild-moderate AE in some clinical trials
Chance of respiratory depression with opioid overdose, generally along with ethanol or sedative ingestion, postoperative scenario or opioid abuse; not commonly reported with the doses used in pain management [76]	No such risk
Risk of opioid induced hyperalgesia with sustained opioid administration [77], [78]	No reports of cannabinoid induced hyperalgesia in animal studies, but some human studies suggest a hyperalgesic effect [67], especially with higher doses of cannabinoids
Opioids induce renal abnormalities in mice [79],[80]	Cannabidiol attenuated chemotherapy induced renal abnormalities in mice [81]
Opioids have been shown to stimulate angiogenesis, which could be harmful in angiogenesis-dependent pathologies including cancer and metastases [82]	Endocannabinoids inhibit angiogenesis [83]
Opioids inhibit apoptosis and promote cell cycle progression via cyclin D1 [82]	Cannabinoids promote apoptosis via ceramide accumulation in transformed cells (especially glioma cells), and may possess anti-tumor activity [22]
Commonly used in cases of acute and severe pain, e.g. post-operative pain, sickle cell crisis, etc.	Shown to be not useful in acute nociceptive pain in humans [84], [85], [86]

Table 5

Clinical Studies with Cannabinoids in Multiple Sclerosis

Agent; route; daily dose	Clinical Condition	Study design	Number. of subjects	Duration of study	Outcome	Adverse effects; reference
Δ9-THC or Cannador® *; oral; self titrated with maximum 25mg Δ9-THC equivalent/d	Multiple sclerosis	Randomized, placebo-controlled multi-center trial	667	15 weeks	No objective improvement in spasticity; improvement in mobility and subjective sense of spasticity	Dizziness, constipation, diarrhea, increased appetite [95]
Sativex® **; oromucosal spray; self-titrated with maximum 48 sprays/d	Multiple sclerosis and other central pain states	Randomized, placebo-controlled, double-blind, single-center trial	66	5 weeks	Significant treatment effect of −1.25 by NRS −11 *** pain scale	Dizziness, somnolence, dry mouth [98]
Δ9-THC; oral;10mg/d of THC or placebo for 3 wks ea	Multiple sclerosis	Randomized double blind placebo controlled, single-center crossover trial with washout	24	9 weeks	20.5% greater reduction in pain from baseline in treatment group	Dizziness, lightheadedness [100]
Δ9-THC or cannabis plant extract; oral; 5–10 mg of THC equivalent or placebo/d for 4 wks ea	Multiple sclerosis with severe spasticity	Randomized, double-blind, placebo-controlled, twofold crossover study	16	12 weeks	No improvement in spasticity or disability by EDSS ****; worsening of functional scores & global perception score	One episode of acute psychosis; no other serious adverse effects [101]
Sativex ®; oromucosal spray; self-titrated to maintain existing analgesia	Multiple sclerosis associated central neuropathic pain	Uncontrolled, open-label, 2-year extension trial (extension of study no 2)	64	2 year	44 % completed 2 yr trial; Mean NRS-11 pain score dropped by 0.9 at 2 yrs	1 each ventricular bigeminy and circulatory collapse; dizziness, nausea, intoxication were common [99]

* Cannador®: Oral capsules containing 2_5 mg of Δ9-THC equivalent, 1_25 mg of cannabidiol, and less than 5% other cannabinoids per capsule. [95]

** Sativex®: Orobuccomucosal spray containing Δ9-THC (27 mg/mL), and cannabidiol (CBD)(25 mg/mL), with a dosage of 100 μL/spray [97]

*** NRS-11:Numerical rating scale for pain [103]

**** EDSS: Expanded Disability Status Scale [104]

Table 6

Clinical Studies with Cannabinoids in Non-Neuropathic Pain

Agent; route; daily dose	Clinical Condition	Study design	Number. of subjects	Duration of study	Outcome	Adverse effects; reference
Nabilone; oral; 1.79 mg/d;	Advanced cancer pain	Prospective observational study	112	30 days	Significant reduction in adjusted pain scores and other symptoms by ESAS * score; decrease in use of morphine-equivalents	Dizziness, confusion, drowsiness, dry mouth; treatment stopped in 6.4% in 24 hrs [106]
Dronabinol; oral; 10 or 20 mg/visit	Chronic non-cancer pain persisting on opioids	Randomized, single-dose, double-blinded, placebo-controlled, crossover trial	30	3 8-hour visits	Significantly better total pain relief at 8 hrs and relief of evoked pain in treatment groups. No difference between 10 & 20 mg	Drowsiness, sleepiness, dizziness, dry mouth [107]
Dronabinol; oral; stepwise self-titrated dose 5–60 mg/d	Chronic non-cancer pain persisting on opioids	Open label extension trial as a continuation of no 11	28	4 wks	Statistically significant decrease in average pain scores from baseline.	Dry mouth, tiredness, sleepiness, drowsiness [107]
Nabilone; oral; 1 or 2 mg at 8 hr intervals	Post-operative pain while on PCA ** morphine	Double-blind, randomized, placebo-controlled, parallel-group pilot trial	41	24 hrs	No decrease in morphine consumption; 2 mg nabilone increased pain	Sedation, euphoria [84]
Cannador®; oral; 5, 10 or 15 mg	Post-operative pain after PCA ** morphine	Multicenter dose-escalation study	20	6 hrs	Significant decrease in rescue analgesia in 10 and 15 mg groups, not in 5 mg group	One serious vasovagal episode with 15 mg dose, led to study termination [108]
Δ9-THC; oral; 5 mg	Post-operative pain after elective abdominal hysterectomy	Randomized double-blind, placebo-controlled, single-dose trial	40	6 hrs	No improvement in SPID *** at 6 h and time to rescue analgesia	Increased awareness of surroundings [109]
Nabilone; oral; escalating dose from 0.5 mg/d to 2 mg/d for 2 wks	Fibromyalgia	Double-blind, randomized, placebo-controlled clinical trial	40	4 wks	Significant improvements in pain by VAS ****, Fibromyalgia Impact Questionnaire score and in anxiety; all benefits lost after 4 wk washout.	Drowsiness, dry mouth, vertigo, ataxia [110]
Sativex®; oromucosal spray; 1–6 sprays/d	Rheumatoid arthritis	Randomized, double-blind, parallel group study	58	5 wks	Significant improvements in pain and quality of sleep; but not in morning stiffness	Dizziness, lightheadedness, dry mouth, nausea [111]

* ESAS: The Edmonton Symptom Assessment System [111]

** PCA: Patient controlled analgesia

*** SPID: Summed pain intensity difference

**** VAS: Visual analogue scale

Table 7

Clinical Studies with Cannabinoids in Neuropathic Pain

Agent; route; daily dose	Clinical condition	Study design	Number of subjects	Duration of study	Outcome	Adverse effects; reference
Smoked cannabis; with 1–8% Δ9-THC 4 times/day, 5 days/week for 2 wks	HIV associated distal sensory predominant polyneuropathy	Double-blind, placebo-controlled, crossover trial with washout	34	6 wks	Difference in decrease in pain intensity by DDS * scale between treatment and control =3.3; 46 % obtained ≥ 30% pain relief with cannabis	Treatment-limiting toxicity in 2 patients [112]
Smoked cannabis; 3.56% THC 3 times/day	HIV associated sensory neuropathy	Randomized placebo-controlled trial	55	5 days	34% had pain reduction vs 17% with placebo. 52% had ≥30% reduction in pain with treatment, vs 25% with placebo	Low incidence of side effects; few had anxiety, sedation, disorientation [114]
Smoked cannabis (with 7% or 3.5% THC)	Central and peripheral neuropathic pain	Randomized, placebo-controlled, crossover trial	38	3 sessions of 6 hrs each	Significant analgesia by VAS **; No difference between 3.5% and 7% groups.	Psychoactive effects, neurocognitive impairment [115]
Sativex®; oromucosal; self-titration	Peripheral neuropathic pain	Randomized, double-blind, placebo-controlled trial	125	5 wks	Mean reduction of 1.48 on NRS-10 *** scale in treatment group vs 0.52 in placebo; improvement in allodynia	Dizziness, nausea, fatigue, dry mouth [116]
Escalating oral doses up to 2 mg nabilone or 240 mg dihydrocodeine/d for 6 wks each	Chronic neuropathic pain	Randomized, double blind, crossover trial with washout	96	14	Mean pain score by VAS ** scale for dihydrocodeine 6.0 less than for nabilone	Tiredness, sleeplessness, sickness [117]
Δ9-THC or CBD or 1:1 mixture of both; sublingual spray	Chronic, mainly neuropathic, pain and associated symptoms.	Initial open-label “n of 1” study, followed by randomized, double-blind, placebo controlled, crossover trial	34	4 wks open label, then 8 wks RCT (2 wks for each treatment and placebo)	28 patients benefited; 11 preferred combination; 14 found THC and combination	Initial drowsiness, dizziness, dysphoria; 1 episode each of vasovagal syncope and hallucination [118]

Agent; route; daily dose	Clinical condition	Study design	Number of subjects	Duration of study	Outcome	Adverse effects; reference
					equally satisfactory	
Sativex® or GW-2000-02 **** sublingual spray; self titrated with maximum 48 sprays/d	Brachial plexus avulsion	Randomized, double-blind, placebo-controlled, three period crossover study	48	3 treatments of 2 wks each	Reduction of 0.58 boxes in mean BS-11 ***** scores with Sativex® and 0.64 boxes with GW-2000-02	Dizziness, somnolence, dysguesia, nausea, feeling drunk [113]

* DDS: Descriptor differential scale for pain

** VAS: Visual analgue scale for pain

*** NRS-10: 10-point Numerical rating scale for pain

**** BS-11: 11-point Box scale for pain

***** GW-2000-02:A THC predominant cannabis extract [118]