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Short Review Article

Spectrum of histopathological lesion in surgically removed appendix

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ABSTRACT

The background to this debate about legitimising cannabis (also called marijuana)—from the plant *Cannabis sativa* for analgesic use is that the drug has been used both therapeutically and recreationally for thousands of years. In Britain doctors were able to prescribe cannabis as recently as 1971and in a 1994 survey 74% of UK doctors wanted cannabis to be available on prescription, as it had been until 1971. The debate has included both the natural chemicals that act on cannabinoid receptors and the synthetic cannabinoid. The synthetic nabilone is the only legally available cannabinoid preparation in the United Kingdom and is licensed solely for use in nausea and vomiting induced by chemotherapy. Delta-9-tetrahydrocannabinol (THC) is the most potent cannabinoid, and although it is available in the United States, it is not licensed for use in the United Kingdom.

Keywords: cannabinoids, marijuana

INTRODUCTION

The recent clamour for wider access to cannabis or cannabinoids as analgesics in chronic painful conditions has some logic. Humans have cannabinoid receptors in the central and peripheral nervous system although the functions of these receptors and the endogenous ligands may yet be unclear. In animal testing cannabinoids reduce the hyperalgesia and allodynia associated with formalin, capsaicin, carrageenan, nerve injury, and visceral persistent pain. The hope then is that exogenous cannabis or cannabinoid may work as analgesics in pain syndromes that are poorly managed. The spasms of multiple sclerosis and resistant neuropathic pain are two obvious targets.

The evidence used in the public debate about the analgesic efficacy of cannabinoids in humans has been gathered in a less than systematic manner and has often been taken from low quality study designs, such as anecdotal reports, questionnaires, or case series. The purpose of this systematic review was to find all of the randomised controlled trials of therapeutic use of cannabis in the management of human pain and then to obtain the best estimates of the efficacy of cannabis compared with either conventional analgesics or placebo. We also sought evidence of adverse effects (safety).

Cannabis is used recreationally because of the euphoria that it produces. The adverse psychological effects (including psychomotor and cognitive impairment; anxiety and panic attacks; and acute psychosis and paranoia) may limit therapeutic use. Other adverse physical effects include dry mouth, blurred vision, palpitations, tachycardia, and postural hypotension.

Decisions about therapeutic cannabinoids, either about medical availability or about future research, should be based on the best available evidence of efficacy, safety, and tolerability. This systematic review was designed to provide that evidence for cannabinoids used as analgesics. Cannabinoid refers to a group of chemicals naturally found in the marijuana plant *Cannabis sativa L.* and includes compounds that are either structurally or pharmacologically similar to Δ(9)-tetrahydrocannabinol or those that bind to the cannabinoid receptors. It was earlier thought that cannabinoids exert their physiologic and behavioural effects via nonspecific interaction with cell membranes. Although anticancer effects of cannabinoids were shown as early as 1975 in Lewis lung carcinoma (ref and references therein), renewed interest was generated little after the discovery of the cannabinoid system and cloning of the specific cannabinoid receptors. The diversified effects of cannabinoids are now known to be mediated through the activation of G-protein–coupled receptors that are normally bound by a family of endogenous ligands, the endocannabinoids. Two cannabinoid receptors have been characterized and cloned from mammalian tissues: the "central" CB_1 receptor and the

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"peripheral" CB_2receptor. CB_1 receptors are found primarily in the brain, specifically in the basal ganglia and in the limbic system, including the hippocampus. They are also found in the cerebellum and in both male and female reproductive systems. CB_2 receptors are almost exclusively found in the immune system, with the greatest density in the spleen.

LITERATURE REVIEW

Trial flow

The results of the searches are presented in the figure. The presentation follows the suggested format provided in the QUORUM statement of the 11 excluded trials, three did not use randomised treatment comparisons, four did not use subjective pain outcomes, two had studied experimentally induced pain, and one was published as a letter and one as an abstract.

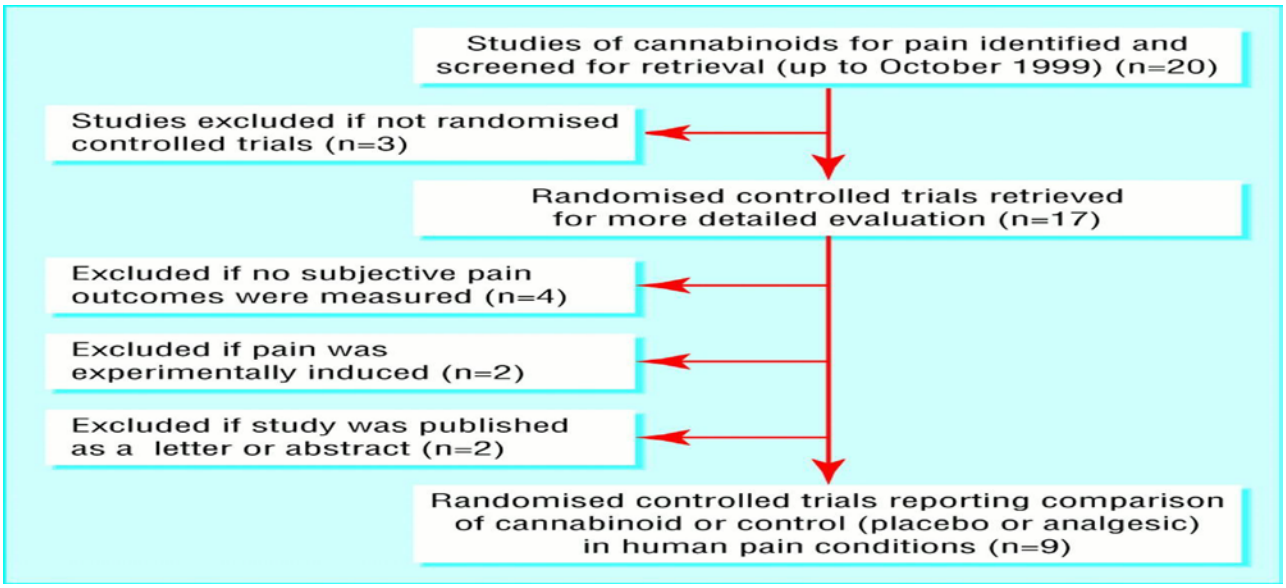

Figure 1:

Study characteristics

Details from nine randomised controlled trials published in seven reports published between 1975 and 1997 were analysed (table). The nine randomised controlled trials comprised a total of 222 adult patients. Five studies that were described in four reports comprised 128 patients with cancer pain. Two studies comprised two patients with chronic non-malignant pain (one patient per trial), and two trials (conducted as a two phase study) comprised six patients with postoperative pain. Follow up was six to seven hours in seven trials and six weeks and five months respectively in the two trials on chronic non-malignant pain. The number of patients in treatment groups ranged from 1 to 37. All studies used a crossover design except the study of postoperative pain. The two studies in chronic pain used an "n of 1 within patient crossover" design. Seven studies described in five reports were single dose evaluations of the analgesic effectiveness of cannabinoids. The median quality score of the trials was 3 (range 3-4) (possible score 0-5). All studies included a placebo group. An adequate method of blinding—for example, tablets of identical shape, colour, and taste was used in all trials where treatments were given orally. There was no explicit description of the method of blinding in the phase 1 and 2 trials comparing intramuscular levonantradol with placebo in postoperative pain.

Acute pain

In the two postoperative pain trials levonantradol was superior to placebo but no more effective than codeine. Such a level of efficacy makes cannabinoids unlikely to be useful, certainly for moderate or severe postoperative pain. Meta-analyses of single dose studies in patients with acute pain found that the number needed to treat for at least 50% pain relief ranged from 2 to 5 compared with placebo for non-steroidal anti-inflammatory drugs and paracetamol. The number needed to treat for codeine 60 mg was much less useful, at 16. If cannabinoids can deliver analgesia only equivalent to codeine 60 mg, with a presumed number needed to treat of about 16 for at least 50% pain relief, they are unlikely to have a place in acute pain treatment.

Cancer and non-malignant pain

No large trials examined cannabinoids in cancer pain and

chronic non-malignant pain. Only two trials had treatment group sizes of more than 30. All five trials in cancer pain were single dose, and four found the cannabinoid as effective as codeine, but with dose limiting adverse effects. Benzopyranoperidine, tested in one trial, was ineffective compared with both codeine and placebo. In chronic non-malignant pain we found two "n of 1 within patient crossover" trials. In a patient with abdominal pain related to familial Mediterranean fever, neither THC nor placebo produced pain relief, but with THC the patient used less additional morphine for breakthrough pain. In Maurer et al's n of 1 study of THC 5 mg for neuropathic pain and spasticity, the reduction in pain intensity was similar to that for codeine 50 mg, but only THC reduced spasticity. We found no trials evaluating smoked cannabis for pain management, but one trial compared the effect of smoked marijuana with smoked placebo on postural balance in patients with spastic multiple sclerosis. The smoked marijuana was associated with subjective improvement of symptoms and with objectively measured impaired posture and balance in all subjects.

Pro-tumor effects of cannabinoids in breast cancer: Although the vast majority of reports published so far show that cannabinoids induce anti-tumor responses not only in breast but in many other types of cancer, a reduced number of articles have reported pro-tumor actions in response to cannabinoids. Thus, McKallip and coworkers found that THC, via CB2 receptors, enhanced the growth of 4T1-derived xenografts and metastases by the inhibition of the anti-tumor immune response Similarly, the growth of xenografted lung tumors was augmented by THC via CB2 receptors49 and by methanandamide via a receptorindependent mechanism. However, other reports demonstrate an important contribution of the immune system in cannabinoid induced anti-tumor action. For example, the growth of melanoma xenografts was inhibited more efficiently by cannabinoids in immune-competent mice than in immune-deficient mice. In addition, a prolonged treatment of immune-competent rats with THC decreased the incidence of tumors and enhanced overall animal survival. Additional studies should be performed to clarify whether cannabinoids activate or inhibit the immune surveillance of tumors. Takeda and coworkers reported that THC enhances the proliferation of MCF-7 cells in culture. Interestingly, both in this case as in the work by McKallip and coworkers, the cells in which pro-tumor effects of cannabinoids were observed expressed undetectable/very low levels of cannabinoid receptors. It would be important to confirm this observation in other breast cancer cell lines to determine whether the lack of CB1/CB2 receptors could be a marker of resistance to cannabinoid anti-tumor action. Additionally, the pro-tumor effect of cannabinoids in certain conditions could be explained by the biphasic effects that these compounds have in multiple processes such as the control of appetite or anxiety. Indeed, we have observed a biphasic effect of cannabinoids in the proliferation of various cancer cell lines: while low doses of cannabinoids promote cell proliferation (unpublished observations), higher doses exert the well described anti-proliferative effect. However, only two works have reported so far pro-tumor effects of cannabinoids in vivo.

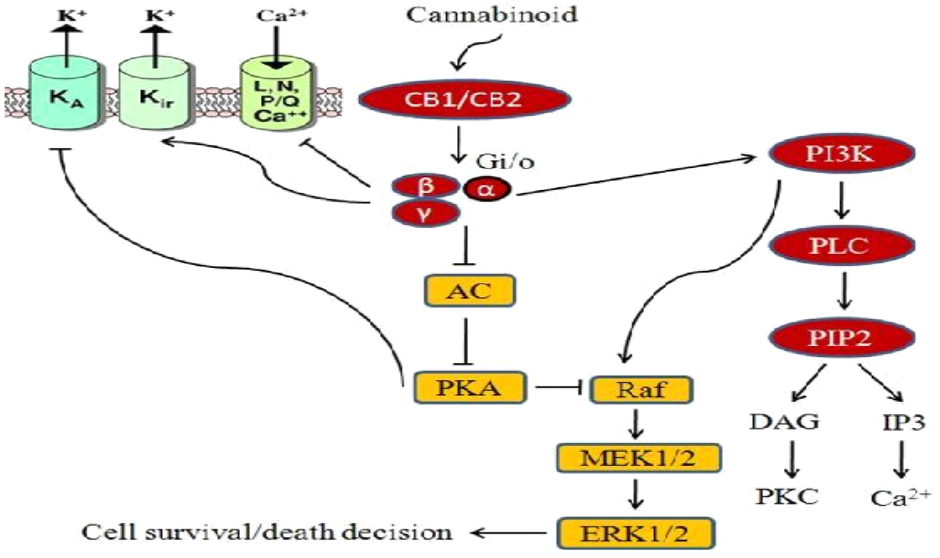

Figure 2: Mechanism of cannabinoid-receptor mediated anti-tumor action in triple-negative breast cancer.

Other potential benefits of cannabinoids for the treatment of breast cancer

A general feature of cannabinoid anti-tumor action in breast and other types of tumors is the lack of toxicity on non-tumor cells. Thus, the inhibition of cancer cell proliferation upon cannabinoid treatment was not evident in non-transformed human mammary epithelial cells. This observation, that has been made as well in other types of cells such glioma cells/astrocytes, skin carcinoma cells/keratinocytes65 and melanoma cells/melanocytes, has not been mechanistically explained yet, but can be mostly attributed to different cannabinoid receptor-triggered intracellular signaling events in cancer versus non-cancer cells rather than to different expression patterns of cannabinoid receptors between both kinds of cells. An additional characteristic of cannabinoids, which may have important clinical implications, is their safety. Cannabinoid-based medicines have been proven very safe in thousands of patients enrolled in multiple clinical trials along the last years and in the cancer patients that use them for the management of pain, nausea and vomiting. Moreover, the safety of THC on recurrent glioblastoma multiforme patients was confirmed in a pilot clinical trial. In all these cases, the most reported side effects were mild/moderate dizziness and fatigue. The most realistic approach to introduce new therapeutic agents in clinical oncology is their combination with standard treatments. There is preclinical evidence showing that the combination of cannabinoids with other established anticancer agents not only does not have negative effects but, instead, induces a synergistic action. For example, temozolomide (the standard therapy for glioma patients) exerted an anti-tumor effect in animal models that was profoundly improved by combination with cannabinoids. Of interest, temozolomide/cannabinoid combinations were very effective in reducing the growth of temozolomide-resistant glioma cell lines. Combination of cannabinoids with other anticancer agents such as gemcitabine, paclitaxel and 5-fluorouracil had synergistic inhibitory effects on the proliferation of cultured pancreatic, gastric and colorectal cancer cells, respectively. As mentioned above, CBD induces marked anti-tumor actions in models of triple-negative breast cancer and other cancers. The addition of this particular compound to potential cannabinoidbased anticancer therapies would have additional benefits. First, it has been reported that CBD enhances the activity of THC in inhibiting the growth of glioma cells in culture and in xenografts, so it is tempting to speculate that this could also be the case for breast cancer. Second, as mentioned above, CBD does not bind with significant affinity to CB1 receptors and, therefore, it does not exert psychoactivity – moreover, it may attenuate some of the psychoactive effects of THC. Third, CBD exerts by itself a plethora of therapeutic effects [including anxiolytic, antipsychotic, antiepileptic, analgesic, anti-inflammatory, anti-ischemic, neuro protective and antiemetic effects3in animal models, some of which might be positive for cancer patient.

ADVERSE EFFECTS

Adverse effects associated with the cannabinoids were common and sometimes severe in six of the eight trials that showed efficacy. The predominant adverse effect seemed to be depression of the central nervous system. Cardiovascular effects were generally mild and well tolerated. Levonantradol was commonly associated with adverse effects (predominantly drowsiness or sedation, or both), of which over half were considered to be moderate or severe. THC 10-20 mg showed a dose-response relation for adverse effects, with depressant effects on the central nervous system occurring in most patients receiving.

Adverse effects of THC. THC showed a dose-response relation for adverse effects—for example, mental clouding, ataxia, dizziness, numbness, disorientation, disconnected thought, slurred speech, muscle twitching, impaired memory, dry mouth, and blurred vision—and at 20 mg was highly sedating in 100% of patients, thus prohibiting its use. THC 10 mg was better tolerated, but the frequency of these adverse effects was still higher than with codeine 60 mg or 120 mg. Reductions in arterial blood pressure occurred compared with placebo, but no more than with codeine. Changes in heart rate were not significant. THC 5 mg was well tolerated in neuropathic pain and did not cause an altered state of consciousness. Levonantradol caused adverse effects in most patients, but none withdrew. The nitrogen analogue of THC did not affect heart rate but caused drowsiness in 40% of patients and was therefore deemed not clinically useful. Benzopyranoperidine caused a similar degree of sedation to codeine but was ineffective as an analgesic.

Efficacy and harm

All of the trials included in this review were conducted since 2003. No trials prior to this date satisfied our inclusion criteria. This review has identified 18 trials that taken together have demonstrated a modest analgesic effect in chronic non-cancer pain, 15 of these were in neuropathic pain with five in other types of pain, one in fibromyalgia, one in rheumatoid arthritis, one as an adjunct to opioids in patients with mixed chronic pain and two in mixed chronic pain. Several trials reported significant improvements in sleep. There were no serious

adverse events. Drug related adverse effects were generally described as well tolerated, transient or mild to moderate and most commonly consisted of sedation, dizziness, dry mouth, nausea and disturbances in concentration.

Limitations

The main limitations to our findings are short trial duration, small sample sizes and modest effect sizes. Thus there is a need for larger trials of longer duration so that efficacy and safety, including potential for abuse, can be examined over the long term in a greater number of patients. It is also important to recognize that cannabinoids may only reduce pain intensity to a modest degree. It remains for the patients to decide whether this is clinically meaningful

CONCLUSION

In conclusion this systematic review of recent good quality randomized trials demonstrates that cannabinoids are a modestly effective and safe treatment option for chronic non-cancer (predominantly neuropathic) pain. Given the prevalence of chronic pain, its impact on function and the paucity of effective therapeutic interventions, additional treatment options are urgently needed. More large scale trials of longer duration reporting on pain and level of function are required.

Cannabinoids are proving to be unique based on their targeted action on cancer cells and their ability to spare normal cells. Variation in the effects of cannabinoids in different cell lines and tumor model could be due to the differential expression of CB1 and CB2receptors. Thus, over expression of cannabinoid receptors may be effective in killing tumors, whereas low or no expression of these receptors could lead to cell proliferation and metastasis because of the suppression of the antitumor immune response.. There is need for further in-depth studies to elucidate the precise mechanism of cannabinoid action in cancer cells. Safety of Δ(9)-tetrahydrocannabinol administration has been determined, and a dose escalation regimen showed that cannabinoid delivery was safe and could be achieved without overt psychoactive effects. In view of the fair safety profile of most cannabinoids together with their antiproliferative action on tumor cells, clinical trials are required to determine whether cannabinoids could be used for the inhibition of tumor growth in a clinical setting. If this could be established, then one can hope that nontoxic, non habit forming cannabinoids could be developed as novel therapeutic agents for the treatment of cancer.

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