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Narrative Review

Cannabinoids and cancer pain: A new hope or a false dawn?

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ABSTRACT

The endocannabinoid system is involved in many areas of physiological function and homeostasis. Cannabinoid receptors are expressed in the peripheral and central nervous system and on immune cells, all areas ideally suited to modulation of pain processing. There are a wealth of preclinical data in a number of acute, chronic, neuropathic and cancer pain models that have demonstrated a potent analgesic potential for cannabinoids, especially in patients with cancer. However, although there are some positive results in pain of cancer patients, the clinical evidence for cannabinoids as analgesics has not been convincing and their use can only be weakly recommended. The efficacy of cannabinoids seems to have been 'lost in translation' which may in part be related to using extracts of herbal cannabis rather than targeted selective full agonists at the cannabinoid CB1 and CB2 receptors.

1. Introduction

The subtle and continuous interplay between the numerous physiological processes required to maintain homeostasis is controlled by a number of regulatory systems, perhaps none more ubiquitous than the endocannabinoid system. This complex biological overseer presents both huge potential for pharmacological manipulation but also huge challenges due to the sheer diversity of its physiological influences. Humans have ingested phytochemical substances which interact with the endocannabinoid system for millennia in the attempt to treat myriad symptoms, but it is only recently that the complex pharmacology of the system and the means to produce synthetic ligands has been realised. To date a significant proportion of research work has focused on the therapeutic potential of harnessing the endocannabinoid system to manage pain, a field of medicine embodied by unmet clinical need and clear requirements for novel therapeutic options. This narrative review provides a germane and current summary of the phytochemistry, pharmacology and physiology of the cannabinoids and the endocannabinoid system and delineates the latest evidence for the use of cannabinoids to attempt to manage pain states especially in cancer patients, a cohort in which pain represents a significant challenge [1]. The pharmacological potential of the endocannabinoid system on potential future directions of preclinical research and the use of novel moieties in the clinical environment is also considered. The methodology of this narrative review comprised a PubMed literature search and Google Scholar search for all types of articles using the search terms 'cannabinoids & pain', 'cannabinoids & cancer pain', 'cannabinoids & neuropathic pain', 'CB1 & pain', 'cannabinoids & phytochemistry', 'cannabinoid receptors', 'cannabinoids & sensory nerves', 'CB1 receptors', 'CB2 receptors', 'cannabinoid pharmacology', 'endocannabinoid system', 'cannabinoids & cancer', 'cannabinoids & tumorigenesis', 'cannabinoids & metastases', 'cannabinoids & GVHD', published between January 1980 and November 2017. Additional articles were identified by manually searching the references of previously identified publications. Articles not written in English were disregarded.

2. Historical perspectives

Cannabis sativa, Cannabis indica and *Cannabis ruderalis* (Family: Cannabaceae) have been cultivated widely since antiquity for use in the production of fibres for rope and fabric, as a food source for both animals and humans and for medicinal applications [2]. Descriptions of its use to treat a broad range of medical conditions reach back millennia, with evidence of the therapeutic consumption of cannabis in ancient Egypt, in Indian *aruvyedic* medicine and in classical Greece and Rome [3]. Over successive centuries, the beneficial effects of the plant and its extracts continue to be mentioned in medical texts including Culpeper's Complete Herbal of 1653 in which it is stated that "The decoction of the root eases the pains of the gout, the hard humours of knots in the joints, the pains and shrinking of the sinews, and the pains of the hips" [4]. By the latter half of the nineteenth century the popularity of medicinal cannabis had reached its peak, with its use advocated by leading medical authorities in patients suffering from a range of conditions including epilepsy, rheumatological complaints, hysteria and 'neuralgia' [5]. The popularity of medicinal cannabis waned in the early 20th

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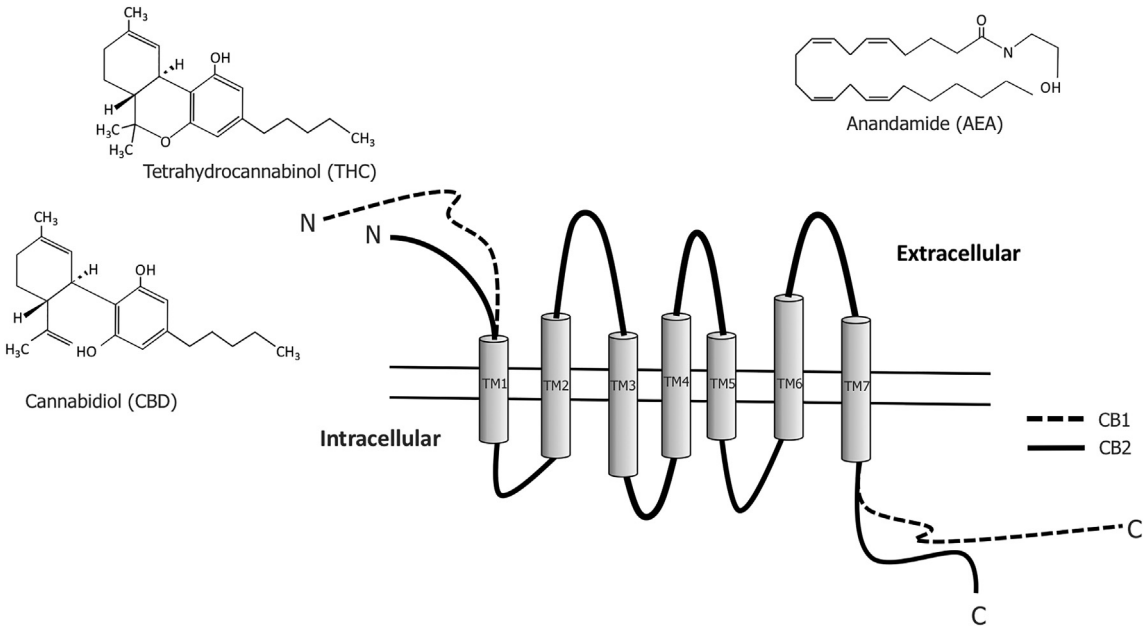

Fig. 1. Schematic showing the CB1 and CB2 cannabinoid receptors and the chemical form of 3 predominant cannabinoids. Cannabinoid receptors are metabotropic G protein-linked structures and comprise 7 transmembrane domains with an extracellular N-terminal and an intracellular C-terminal. Binding of a ligand results in G protein activation, which leads to the inhibition of adenylate cyclase and voltage-gated calcium channels, the activation of mitogen-activated protein kinase and of inwardly rectifying potassium channels.

century (Cannabis was removed from the British Pharmacopeia in 1932 and the American Pharmacopeia in 1941) as a result of a better understanding of the pathophysiology of disease and an expansion in the number of effective therapeutic options available [6].

These advances coincided with a greater governmental awareness of the illicit use of cannabis and the subsequent introduction of laws which criminalised its cultivation, refinement and consumption. This process was exemplified by the adoption of emotive language such as "Marijuana is the most violence-causing drug in the history of mankind" voiced during testimony to the United States Congress, and the subsequent levy in 1937 of a $100 per ounce tax that effectively outlawed cannabis in the United States [7]. In 1970 cannabis was classified as a class I drug, legislation indicating a high potential for abuse but also stating that it had no accepted medical use.

The story of medicinal cannabis may easily have finished at this point, however in recent times the combination of an improved understanding of the neurobiology of pain and a requirement for the development of novel analgesic agents has triggered a burgeoning interest in the use of cannabis for therapeutic purposes. This has led to a situation where in some legislative domains, illicitly consumed cannabis remains illegal, whilst purified extracts (or industrially synthesised analogues) are permitted when used medicinally.

3. Phytochemistry of *Cannabis sativa*

The phytochemical profile of the various strains of *cannabis* is complex; with many hundreds of substances produced, some of which, namely the terpenophenolic cannabinoid compounds, are unique to *Cannabis sativa* [8]. Of the > 70 cannabinoids produced within the plant, the most bountiful are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [9]. These substances differ in their pharmacological effects, with THC acting as a potent psychoactive agent and CBD possessing anxiolytic and analgesic properties [10]. There is great variability in the levels of differing cannabinoids between distinct subspecies and cultivars (termed chemotypes) of *Cannabis sativa*. Drug forms of cannabis (marijuana and hashish) have high levels of THC, a situation established through a process of selective breeding and refined cultivation techniques, whilst cannabis grown for industrial and agricultural purposes (hemp) has a low THC content [11].

4. Pharmacology of cannabinoid receptors

The pharmacological effects of ingested cannabinoid compounds are predominantly mediated via interaction with the endocannabinoid system. The endocannabinoid system is a physiologically omnipresent regulatory system which comprises endogenous cannabinoids (endocannabinoids), cannabinoid receptors and the enzymes involved in synthesising and metabolising endocannabinoids [12]. The system plays an important role in neuro- and immunomodulatory effects which impact upon the homeostasis of processes relating to appetite [13], motor function [14], fertility [15] and pain sensation [16].

The majority of cannabinoid and endocannabinoid effects are mediated by two G protein-coupled cannabinoid receptors, termed the CB1 and CB2 receptors. These receptors are found widely throughout the body but with some differences in their distribution; CB1 receptors are found abundantly in the central and peripheral nervous system, whilst CB2 receptors are predominantly expressed on immune cells where they modulate cytokine release [17]. The ubiquity of expression of cannabinoid receptors in multiple areas of the central and peripheral nervous system explains the apparent potential utility for exogenous cannabinoids in a number of different human physiology and pathologies including, but not limited to, the modulation of memory, appetite, development of multiple sclerosis and different types of shock [18].

Cannabinoid receptors are metabotropic in nature, linked to their downstream effectors by G-protein mediated signal transduction. Structurally both CB1 and CB2 comprise seven transmembrane protein domains [19] (Fig. 1), which predominantly couple to the inhibitory G proteins Gi and Go [20]. The intracellular consequences of G protein activation include the inhibition of adenylate cyclase and certain voltage-gated calcium channels, the activation of mitogen-activated protein kinase (MAP kinase) and of inwardly rectifying potassium channels [21]. In the central and peripheral nervous system, the net effect of these processes is to dampen neuronal excitability and to negatively modulate neurotransmission. Interestingly there is also evidence that CB1 receptors may induce morphological changes in neurones including inhibition of synapse formation and retraction of neurites [22]. In immune cells, CB2 receptor activation results in a slew of suppressive effects including impaired antigen presentation, reduced cytokine release and disruption of immunocyte migration [23].

Agonists acting at CB receptors can be divided into 3 broad groups; (1) the arachidonic acid -derived endogenous ligands arachidonoylethanolamide (anandamide, ANA) and 2-arachidonoylglycerol amide (2-AG) - selective agonists for the CB1 and CB2 receptors, respectively [24]; (2) the plant derived 'phytocannabinoid' THC which activates both CB1 and CB2 receptors [25]; and (3) the rapidly expanding stable of synthetic compounds such as the THC analogues nabilone and (−)-11-hydroxy-Δ8- THC-dimethylheptyl (HU-210), both of which have relatively high affinity for CB1 and CB2 receptors [26]. In contrast, the phytocannabinoid CBD displays minimal affinity for the CB1 and CB2 receptors, and may, at certain concentrations act as a partial agonist at the CB2 receptor, inhibiting the effect of other ligands such as THC [27]. Due to this limited receptor efficacy, interest has focused on identifying alternative mechanisms through which CBD exerts its biological effects. These are thought to include the inhibition of anandamide reuptake, the activation of the transient receptor potential of vanilloid type-1 (TRPV -1) and transient receptor potential cation channel, subfamily A, member 1 (TRPA-1) receptors and the antagonism of the transient receptor potential cation channel subfamily M, member 8 (TRPM8) receptor and the 'orphan' cannabinoid receptor GPR55 [28,29]. Other endogenous cannabinoids include palmitoylethanolamide (PEA) which is notable by its preclinical analgesic efficacy (reversible by CB2 receptor antagonism), yet has very little affinity for the CB2 receptor [30,31]. This indirect action of cannabinoid receptor-mediated analgesia has been suggested to be secondary to inhibition of the breakdown of other endocannabinoids, in the so-called 'entourage effect' [33]. This entourage effect has also been implicated in some cannabinoid mediated anti-cancer actions [34].

The endocannabinoid system is distinct from many other innate homeostatic systems in the fact that its endogenous ligands display a degree of receptor promiscuity, acting on targets other than the CB1 and CB2 receptors. The most notable of these receptors is the TRPV-1 receptor – a non-selective cation channel which structurally comprises six transmembrane spans with a central pore. TRPV-1 receptors detect noxious thermal stimuli and gate at temperatures in excess of 42°C, the receptors are expressed in sensory neurones present in both the peripheral and central nervous system [32]. The endocannabinoid ANA (but not 2-AG), activates the TRPV-1 receptor, which is often co-localised with CB1 and CB2 receptors. It is thought that subsequent 'crosstalk' which occurs between different activated receptor types may promulgate the ability of a single mediator to possess multiple pharmacological effects, thereby broadening the physiological impact of the endocannabinoid system [33]. Indeed it has been postulated that activity of compounds at both the cannabinoid and TRPV1 receptors could provide potential potent analgesia [34].

The enhancement of endogenous cannabinoid function has also been suggested as a therapeutic strategy. For example, inhibiting the breakdown of endogenous cannabinoids by acting on fatty acid amide hydrolase (FAAH) has some evidence of analgesic efficacy [35].

5. Evidence for cannabinoids in pain processing

Pain, an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, represents a major area of unmet clinical need, due both to its ubiquity at a population level and the relative lack of efficacious treatments available. There has been much interest in the role played by the endocannabinoid system in the sensory pathways related to the transmission, modulation and perception of pain and a number of compounds acting on the system have been examined clinically as potential analgesic agents.

It has long been known from in vivo immunohistochemical work in rodents that the CB1 receptor is expressed widely in central and peripheral neurones which play a key role in pain perception [36] such as in the dorsal horn of the spinal cord [37]. The prevalent nature of the CB1 receptor within pain transmitting pathways presents an attractive target for the development of novel analgesic agents, based on the rationale that the systemic administration of cannabinoids would induce diffuse inhibition of pain signaling pathways. However, the very ubiquity of the receptor within the nervous system means that their activation, especially in higher brain centres, may also potentially result in deleterious side effects. Work in the field has predominantly focused on the use of refined extracts of either phytocannabinoids derived from *Cannabis sativa* or synthetic analogues of phytocannabinoids and to date few agents have been successfully introduced to clinical practice.

6. Preclinical data for cannabinoids in pain

The use of cannabis and its derivatives for recreational and therapeutic gain long predates the identification and characterization of cannabinoid receptors and endogenous ligands. Endocannabinoids have a role in many different physiological processes in the body which are often involved in homeostasis [33]. Teasing out the complex pharmacology has highlighted the possibility of achieving therapeutic benefit such as analgesia but without risking the 'high' which is the basis of recreational use, but which is not welcome in clinical applications. This may potentially be realised by targeting the CB2 receptor which is expressed predominantly on immune cells in contrast to the CB1 receptor expression which is primarily (but not exclusively) neuronal.

There are a wealth of preclinical data that supports the role of cannabinoids as analgesics [38]. Both CB1 and CB2 receptors have been implicated and shown to be useful in many different types of preclinical pain models. For example, the analgesic action of the mixed CB1/CB2 agonist synthetic cannabinoid WIN55,212-2, was inhibited by antagonism at both CB1 and CB2 receptors in a model of inflammatory pain [39]. Interestingly there was also evidence of a difference in mechanism for a cancer pain model by which the CB2 receptor antagonist did not modulate the analgesic effect suggesting the CB1 receptor is the more important target. In a fibrosarcoma cancer pain model, both a CB1 receptor agonist and the CB2 receptor agonist reduced tumor induced mechanical hyperalgesia [40]. Nevertheless, there are also robust data implicating the role of the CB2 receptor in other pain types including cancer bone pain [41]. Many studies have also demonstrated the potential for a peripheral site of action, with analgesic effects being mediated by local administration of agonists [42]. There is also evidence that cannabinoids may act synergistically with opioids. Part of this is related to a direct synergistic analgesic effect but cannabinoids may also reduce or prevent opioid tolerance a process which may also be mediated by the CB2 receptor [43].

However, although animal studies have been able to use selective CB1 and CB2 receptor agonists (and indeed antagonists) these are not readily available in human trial or clinical settings. Further difficulties in translating robust preclinical data into useful pain treatments include the legal status of cannabinoids. As previously stated, in the United States of America, Cannabis is a schedule 1 drug (high potential for abuse and no accepted medical use) whilst in the United Kingdom their classification (in the group of drugs defined as "dangerous or otherwise harmful") oscillates between class B and class C drug (less capacity for harm) - cannabis is currently a class B drug. Partly because of these legislative factors, and partly because of the potential to minimise central unwanted side effects, the CB2 receptor has been postulated as a target of choice [44].

The CB2 receptor is also a G protein coupled receptor which inhibits adenylate cyclase. As discussed, CB2 receptors are expressed on immune cells (as well as microglia) and occasionally on neurones, especially after damage. A significant problem with this receptor is that few CB2 specific agonists exist, and most which act at the CB2 receptor are selective (not specific) meaning that exclusion of the psychoactive neuronal CB1-mediated actions is difficult. The situation is further complicated by 'functional selectivity'of ligands by which different agonists at the CB2 receptor have differential effect on signaling pathways (e.g. adenylate cyclase, MAP kinase) [45].

7. Evidence for neuropathic pain and cancer-related neuropathic pain

Cannabinoids have been found to be effective in preclinical studies of several models of neuropathic pain including nerve injury and diabetic neuropathy [46,47]. Although many of the earlier studies implicated an analgesic action at the CB1 receptor, others have demonstrated the CB2 receptor to be at least as important in some neuropathic pain models [48,49]. Interestingly these studies also showed little in the way of centrally mediated and unwanted side effects, thereby demonstrating real potential for having therapy without 'recreation'.

CB1 and CB2 receptors have been implicated in the reduction of pain behaviours in a model of chemotherapy induced neuropathic pain [35,50]. The local anti-hyperalgesic action of ANA in cisplatin induced CIPN was mediated by the CB1 receptor [51]. In addition, after cisplatin-induced hyperalgesia, there was a reduction in local paw concentration of ANA. Increasing local concentration of anandamide by using an inhibitor of ANA hydrolysis also caused reduction in hyperalgesia via the CB1 receptor. Cisplatin-induced reduction of in vitro neuronal growth was also prevented by ANA [51]. However, two studies of paclitaxel-induced CIPN identified the CB2 receptor as being key [52,53]. Deng's study used CB1 receptor knockout mice (where there is no functional CB1 receptor) and found that a mixed CB1/CB2 agonist was active despite the lack of CB1 receptor. One further advantage of targeting this receptor is that in contrast to the CB1 receptor, the CB2 receptor does not appear to display tolerance with repeated dosing [54].

8. Evidence for efficacy of CBs in models of cancer pain

In several models of pain caused by cancer, cannabinoids have shown to be effective in reducing pain behaviours by a peripheral action and at both CB1 and CB2 receptors [42,55]. In the squamous cell carcinoma model, local administration of a non-selective CB1/CB2 and a selective CB2 agonist both attenuated mechanical hyperalgesia. Of note, CB1 receptor expression was increased in dorsal root ganglia ipsilateral to the cancer [55]. Hyperalgesia induced by fibrosarcoma bone cancer was reduced by local ipsilateral administration of WIN 55,212, but not when injected into the contralateral paw [56]. Moreover, the most effective dose of WIN 55,212–2 (CB1/CB2 agonist) did not cause any central adverse effects (catalepsy). One mechanism implicated for this anti-hyperalgesic action on cancer pain is direct CB1-induced inhibition of nociceptive C fibres [57] and the CB2-mediated release of endogenous opioids from keratinocytes has also been postulated [55].

Similar to the findings for CIPN, local AEA concentration was not only associated with the pain behaviours in osteolytic bone cancer but both the local injection of ANA and inhibition of FAAH reduced mechanical hyperalgesia [58]. These data highlight the potential importance of endocannabinoids in pain from cancer per se and from the treatment of cancer (CIPN). It also gives credence to the potential therapeutic mechanism of increasing local endocannabinoid levels by inhibition of their breakdown. Furthermore, the targeting of CB2 receptors or peripheral CB1 receptors (which may be upregulated in some cancer pain types) insinuates the possibility of divorcing analgesia from unwanted central side effects for cancer pain.

9. Clinical evidence for cannabinoids in cancer pain

Extracts of herbal cannabis have been used in many different types of pain and remain the best studied cannabinoids in clinical trials. Although some of these data involve smoked cannabinoids, we feel that this route of administration would not ever get regulatory approval and we have not included discussion of such studies.

It has been suggested that 40% of pain in cancer patients is neuropathic and therefore cannabinoid efficacy in neuropathic pain may be a potential indicator of utility in cancer patients. Meng identified 11 RCTs that examined cannabinoids in several central and peripheral neuropathic pain states, and concluded that cannabinoids could achieve a small reduction in pain scores but the GRADE recommendation was weak [59]. There was also some evidence for efficacy of cannabinoids in other secondary measures such as quality of life and sleep.

There have been several investigations which used a mixture of Δ^9-tetrahydrocannabinol and cannabidiol (approximately 1:1) known as Sativex or Nabiximols. This preparation is licensed in Canada for cancer pain but in the United Kingdom is only licensed for pain associated with multiple sclerosis (MS). Sativex is administered by an oral mucosal spray.

A large, recently published review examined the evidence for cannabinoids in all medical uses [60]. The authors identified 3 papers investigating cancer pain, two of which used a 1:1 combination of tetrahydrocannabinol:cannabidiol (THC:CBD) extract (Nabiximols or Sativex) [61,62] and another (for chemotherapy induced neuropathic pain) used a purified cannabinoid extract [63]. Both studies included patients with advanced cancer pain with pain numerical rating scale (NRS) scores of > 4 despite opioid treatment. In one, the primary outcome of 30% improvement with Nabiximols was no different to the control group, although some of the secondary measures showed some advantage of the lower dose Nabiximols over control [61]. The other study compared Sativex to THC alone and control. Only Sativex demonstrated a statistically significant improvement of the primary outcome (change in average pain score from baseline) of -1.37 vs. -0.69 in controls. 23 of the 60 patients (38%) in the Sativex group achieved the secondary measure of 30% improvement in NRS compared to 12/59 (20%) in controls. In all the studies for all the medical indications, cannabinoid treatments had a greater risk of any adverse events compared to controls (OR 3.03 [2.42–3.8]) including serious adverse events (OR 1.41 [1.04–1.92]) and study withdrawal due to adverse events (OR 2.94 [2.18–3.96]). These data lead the authors of the meta-analysis to suggest that Nabiximols 'may be beneficial' for cancer pain. However, further similar trials have not strengthened the underwhelming case for the use of cannabinoids in this clinical application.

The effect of self-titration over 2 weeks on 397 patients with advanced cancer and refractory pain (despite optimal opioid treatment) was investigated and compared to placebo [64]. Sativex was associated with a reduction in average NRS pain score of 10.7% compared to 4.5% in the placebo group which was not statistically significant. Subgroup analysis revealed some of the secondary outcomes (such as quality of life) were improved, and these were more likely in participants from the United States. Two additional RCTs, both reported in a single paper, examined cancer pain patients also on 'optimized' opioid therapy (≥ 90 mg/day morphine equivalents) but who still reported average pain ≥ 4 and ≤ 8 on a 0–10 NRS [ref]. One study was of enriched enrolment design [65]. In the enriched enrolment trial of the 406 patients that entered the study, nearly half withdrew in the initial titration phase (a third of which were due to adverse events) and a quarter of the remaining patients withdrew in the randomized phase with a similar proportion citing adverse events. The primary outcome of mean average pain scores actually increased from 3.2 to 3.7 in the treatment group. Even the controversial statistical practice of 'sub groups analysis' could not find any significant difference in the primary outcome between Sativex and control. The other study (in the same single paper) used similar methodology but without enriched enrolment. Of the 30% who withdrew from the Sativex group, 60% were due to adverse effects. The primary outcome of percent improvement in average pain NRS score from baseline to end of treatment was only 7.2% which was even less than the 9.5% in the control group. Even a subgroup analysis that revealed patients from the USA < 65 years old experience greater benefit from Sativex than control (11.2% vs. 4.8%) was not statistically significant. Adverse effects were reported by over 60% in both Sativex and control groups.

Overall the results of these trials do not make a compelling argument for the use of these cannabis extracts. Perhaps the adage from

Andrew Moore of 'Expect analgesic failure; pursue analgesic success' would be the most pragmatic use of the available data [66].

10. Cannabinoids for other symptoms in cancer patients

Are there any other indications for the therapeutic use of cannabinoids in patients with cancer? In a systematic review in 2001 that included 30 trials of cannabinoids in chemotherapy-induced nausea and vomiting, Tramér concluded that cannabinoids could be more efficacious than some alternative antiemetics such as prochlorperazine and metoclopramide and suggested a number needed to treat of 6 for nausea and 8 for vomiting [67]. A more recent Cochrane review concluded cannabinoids were more effective than placebo in completely stopping nausea and vomiting, and comparable in action to other antiemetics similar to those indicated in the Tramér paper, such as prochlorperazine and metoclopramide. As the authors warned however, there were no comparative trials with the more commonly used and more efficacious 5-HT 3 antagonists [68]. The previously discussed recent large meta-analysis identified 28 studies examining cannabinoid use for the treatment of nausea and vomiting from chemotherapy [60]. Approximately half the studies investigated the use of nabilone. Although all studies demonstrated some benefit of the cannabinoid, only 3 studies were able to be pooled in a meta-analysis. Overall these 2 studies of dronabinol and 1 of Nabiximols demonstrated reduced nausea and vomiting compared to placebo with an odds ratio of 3.82 (CI 1.55–9.42).

Although dronabinol is licensed in the United States for appetite stimulation in HIV patients, examination of cannabis extract and THC in patients with cancer related anorexia found no benefit on appetite compared to controls [69]. This is actually a similar negative result found by the Cochrane review looking at dronabinol for appetite stimulation in HIV patients [70]. As with pain, these data are far from conclusive and although cannabinoids may have some efficacy in nausea and vomiting, their efficacy has not been compared against the current clinical standard. Cannabinoids remain as a potential option, perhaps in nausea and vomiting which is refractory to other widely used agents, but robust evidence in their favour is sparse.

11. Cannabinoids as anticancer agents

Due to the well-documented immunomodulatory effects of cannabinoids, the influence of these agents on tumorigenesis, metastatic spread and the control of associated oncological sequelae such as Graft-Versus Host Disease (GVHD) has been investigated. This is a scientifically intriguing area – with in vitro and in vivo work with cancer cell lines and animal models of cancer which demonstrate both cancer regression and progression, hinting at the complexity of the mechanisms involved. The exact effect of cannabinoids on tumor growth appear to be cancer-specific and often mediated by 'off receptor' pathways – not involving the CB1 or CB2 receptors. For example, the presence of high levels of the receptor GPR55 is associated with more aggressive forms of breast and pancreatic cancer and glioblastoma, whilst AEA mediated activation of the receptor induces apoptosis in cholangiocarcinoma cells [71]. There have been a number of attempts both in the pre-clinical and clinical setting to harness the immunosuppressive effects of cannabinoids to control GVHD – a major cause of morbidity following allogenic hematopoietic cell transplantation. In a mouse model of GVHD, THC was effective in both preventing and treating the condition [72], whilst in a recent human phase II trial, the combination of CBD with standard anti-GVHD prophylaxis proved more efficacious than usual care alone at reducing the incidence of acute GVHD [73]. Further work investigating this clinical application of cannabinoids is clearly warranted.

The scale of the work conducted regarding the influence of cannabinoids on cancer is extensive and a comprehensive summary outwith the scope of this paper, there are several excellent recent reviews of this topic to which the reader is directed [74,75].

12. Where are we now?

Despite the wealth of pre-clinical data demonstrating both CB1 and CB2 agonists as potentially effective analgesics in a number of inflammatory, neuropathic and cancer pain states, clinically cannabinoids have been found wanting. Use of available cannabinoids such as nabilone and dronabinol for patients with cancer pain and associated symptoms is sporadic and although Sativex is available on a named patient it is currently not widely used in the UK (MS pain notwithstanding). This translational gulf could be in part accounted for by the difference in the underlying pharmacology of the preclinical and clinical approaches. Pre-clinically, research has been able to use selective agonists whereas clinically most of the data is from phytocannabinoids derived from herbal cannabis with less affinity and some agents displaying only partial agonist effect at mixed cannabinoid receptors. The inability of these cannabinoids to differentiate between therapeutic affect and side effect also limits their clinical utility. Difficulties of legislation have also made clinical research less than straight forward. It is difficult to argue any more vociferously than to agree with commentators and offer a weak recommendation for the use of cannabinoids in cancer pain. The possibility of adverse effects further tempers this fragile endorsement. It is ultimately disappointing that such a potent endogenous modulatory system cannot be better appropriated to achieve meaningful analgesia. Perhaps it is time to perform a complete 'reboot' of cannabinoid research and pursue the use of selective, synthetic full agonists at the CB1 and CB2 receptors.

Conflict of interest statement

There are no conflicts of interest.

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