Medical Hypotheses (2006) **66,** 234–246

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medical hypotheses

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A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol

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Received 15 August 2005; accepted 18 August 2005

Summary This study examines the current knowledge of physiological and clinical effects of tetrahydrocannabinol (THC) and cannabidiol (CBD) and presents a rationale for their combination in pharmaceutical preparations. Cannabinoid and vanilloid receptor effects as well as non-receptor mechanisms are explored, such as the capability of THC and CBD to act as anti-inflammatory substances independent of cyclo-oxygenase (COX) inhibition. CBD is demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right. In modern clinical trials, this has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain. Prospects for future application of whole cannabis extracts in neuroprotection, drug dependency, and neoplastic disorders are further examined. The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported.

Introduction

Cannabinoids refer to a heteromorphic group of molecules that demonstrate activity upon cannabinoid receptors and are characterised by three varieties: endogenous or endocannabinoids, synthetic cannabinoids, and phytocannabinoids, which are natural terpenophenolic compounds derived from *Cannabis* spp.

In recent years, scientists have provided elucidation of the mechanisms of action of cannabis and THC with the discovery of an endocannabinoid ligand, arachidonylethanolamide, nicknamed anandamide, from the Sanskrit word *ananda*, or ''bliss'' [1]. Anandamide inhibits cyclic AMP mediated through G-protein coupling in target cells. Early

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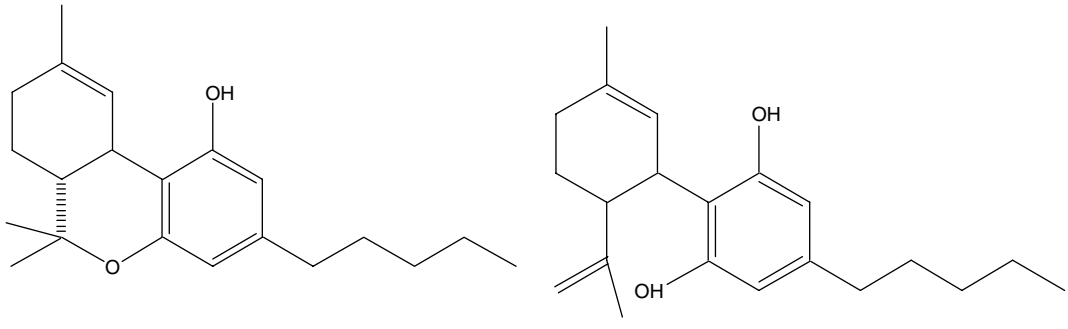
0306-9877/$ - see front matter
doi:10.1016/j.mehy.2005.08.026

testing of its pharmacological action and behavioural activity indicate similarity to THC [2], and both are partial agonists on the CB_1 receptor. Pertwee [3] has examined the pharmacology of cannabinoid receptors in detail. CB_1 receptors are most densely demonstrated in the central nervous system, especially in areas subserving nocicecption, short-term memory, and basal ganglia, but are also found in the peripheral nerves, uterus, testis, bones and most body tissues. CB_2 receptors, in contrast, are mostly found in the periphery, often in conjunction with immune cells, but may appear in the CNS particularly under conditions of inflammation in association with microcytes. Additional non-CB_1 and non-CB_2 receptors in endothelial and other tissues are hypothesised [4], but not yet cloned. Further research has elucidated analgesic mechanisms of cannabinoids, which include effects on numerous neurotransmitter systems and interactions with the endogenous opioid system.

This paper will focus on the biochemical and clinical effects of two phytocannabinoids, Δ^9-tetrahydrocannabinol (THC) (Fig. 1), the main psychoactive component of cannabis, and its non-psychoactive but highly physiologically relevant isomer, cannabidiol (CBD) (Fig. 1). While it was originally thought that CBD was the metabolic parent to THC in the cannabis plant, rather, they are both biosynthesised as THCA and CBDA from a cannabigerolic acid precursor (Fig. 2) according to genetically determined ratios [5], and then decarboxylated by heat or extraction to produce THC and CBD proper. It is interesting to note that the phytocannabinoids can be considered as half-siblings to the essential oil terpenoids with which they share a geranyl pyrophosphate precursor in the glandular trichomes of the plant where they are produced. It is felt by some authorities that these terpenoids share important modulatory and pharmacological effects with trace cannabinoids [6] in an elegant 'entourage effect' [7] that may account for synergistic activity of cannabis extracts over that of isolated components. Therapeutic benefits are thus added, whilst some adverse effects are attenuated. In this regard, Carlini [8] determined that cannabis extracts produced effects two or four times greater than that expected from their THC content, based on animal and human studies. Similarly, Fairbairn and Pickens [9] detected the presence of unidentified 'powerful synergists' in cannabis extracts, causing 330% greater activity in mice than THC alone. An unidentified component of the plant (perhaps linalool?) also showed anticonvulsant properties of equal potency to cannabinoids [10]. Finally, although anecdotal to some degree, extensive surveys in the USA comparing patients' subjective responses with synthetic THC as Marinol® supports a preference for whole cannabis products [11]. In most instances, synthetic THC is considered by patients to be more productive of intoxicating and sedative adverse effects [12], characterised by the authors as (p. 95), 'dysphoric and unappealing'.

The effects of THC are well known, and include analgesia, intoxication, short-term memory loss, muscle relaxant and anti-inflammatory effects [3,13] (summarised in Fig. 3, with corresponding references).

The pharmacological profile of CBD has received three recent excellent reviews [14,15]. Briefly stated, CBD has anti-anxiety actions [16], anti-psychotic effects [17], modulates metabolism of THC by blocking its conversion to the more psychoactive 11-hydroxy-THC [18], prevents glutamate excitotoxicity, serves as a powerful anti-oxidant [19], and has notable anti-inflammatory and immunomodulatory effects [20] (summarised in Fig. 3 with corresponding references). Notably, CBD has recently been shown to act as a TRPV1 agonist of potency equivalent to capsaicin, while also inhibiting reuptake of anandamide and its hydrolysis [21]. Thus, CBD may prove to be the first clinical pharmaceutical to modulate endocannabinoid function.



delta-9-tetrahydrocannabinol (THC) cannabidiol

Figure 1 Structures of THC and CBD.

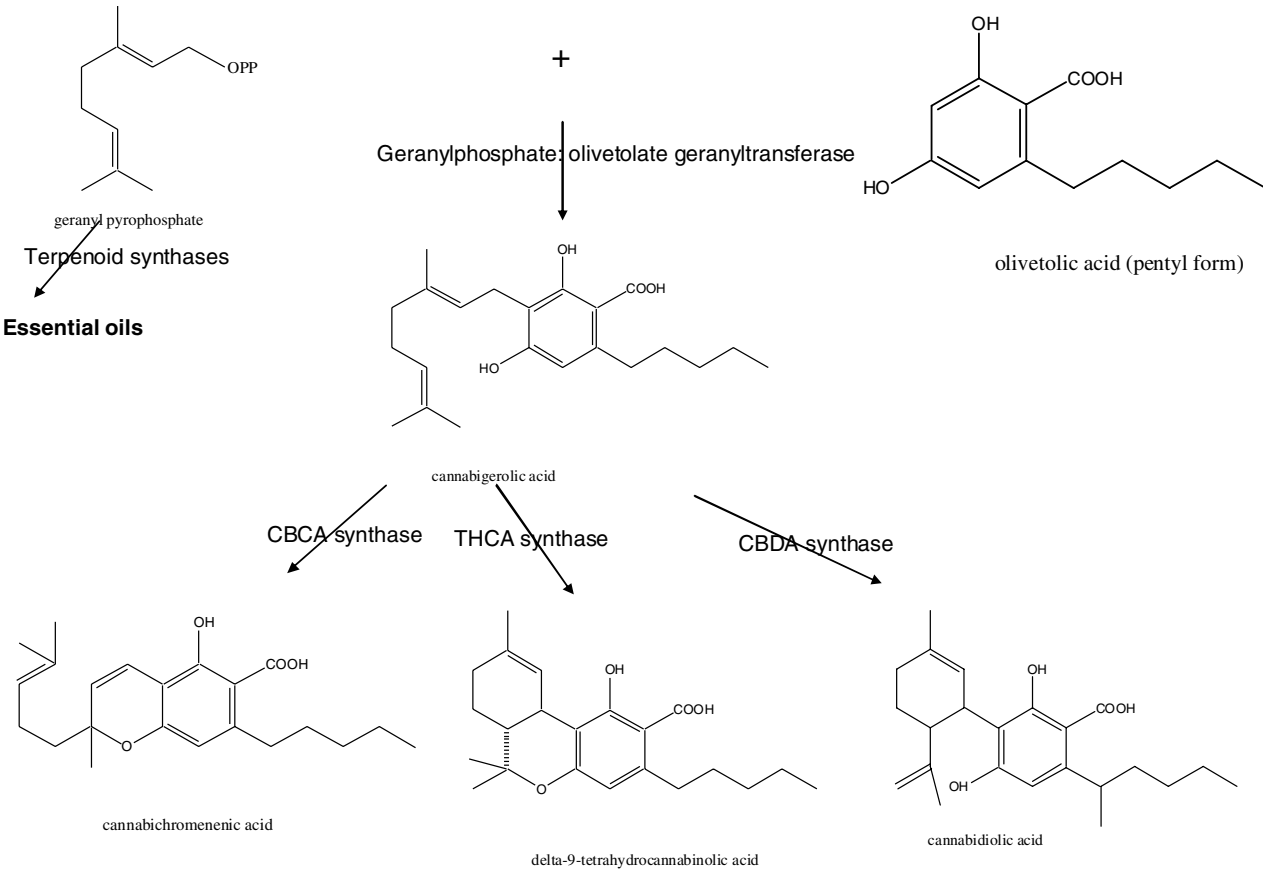


Figure 2 Biosynthetic pathways of pentyl phytocannabinoids (adapted and revised from de Meijer et al. [5]).

The remainder of this paper will focus on the interactions of the two compounds when administered simultaneously and explore the theoretical advantages of so doing in clinical application.

A review of animal studies of simultaneously administered THC and CBD

A great deal of the early research pertaining to interactions of THC with other phytocannabinoids was performed in Brazil in the 1970s. The seminal work was that of Karniol and Carlini [22] who examined various animal species with differing low-moderate doses of THC and CBD administered IP. To summarise, CBD blocked certain effects of THC: catatonia in mice, corneal arreflexia in rabbits, increased defaecation and decreased ambulation in rats in the open field after chronic administration, and aggressiveness in rats after REM-sleep deprivation. In contrast, CBD potentiated THC analgesia in mice and the impairment of rope climbing in rats. The authors hypothesised that CBD interacted via a dual mechanism: potentiating the depressant effects of THC while inhibiting its excitatory and emotional effects.

In an Australian study of oral dosing [23], the 'abdominal constriction response' to formic acid in mice, CBD antagonised the analgesic effect of THC. The pertinence of this model to current clinical models in humans is unclear.

In a rat study with implanted brain electrodes [24], CBD 20 mg/kg IP decreased slow-wave sleep latency. The author posited a hypnotic effect, but given the experimental setting, an analgesic response may have been operative.

In a complex protocol assessing variable-interval performance in rats after food deprivation [25], the authors assessed that a 'marijuana extract distillate' depressed performance at most levels of deprivation, but that IP CBD potentiates that depression only at high levels of deprivation. In subsequent related rat experiments [26], a 20-fold CBD:THC ratio antagonised THC effects on variable-interval performance, while fivefold ratios seemed to potentiate THC effects. The implications for therapeutic usage in humans are not clear from these data.

An American group [27] implicated CBD as contributing to mortality and seminiferous tubule degeneration in an usual protocol employing smoke exposure in rats to a Turkish cannabis strain. No separation of CBD vs. CBC (cannabichromene) was achieved, however. These results would not be contrasted to the extremely low-level mortality and histological changes seen in current animal toxicity studies performed with cannabis based medicine (CBM) combining THC and CBD [28].

In a study of rats trained to distinguish THC in a T-maze [29], CBD 40 mg/kg prolonged running time, but did not affect the animals' choices. This high dose was employed because (p. 140), ''this dose was the minimum capable of interfering with the discriminative performance of rats that that received 5 mg/kg Δ^9-THC''. This slowing of run time also disappeared within 72 h.

In a recent study in rats [30], a CBD-rich extract containing THC did not affect spatial working mem-

Effect	THC	CBD	References
Receptor/Non-Receptor Effects			
CB_1 (CNS/PNS receptors)	++	±	Pertwee (104)
CB_2 (peripheral receptors	+	±	Showalter (105)
Vanilloid ($TRPV_1$) receptors	-	-	Bisogno (21)
Anti-inflammatory	+	+	Hampson (73)
COX-1, COX-2 inhibition	-	-	Stott (106)
Immunomodulatory	+	+	Cabral (107),Malfait (20)
CNS Effects			
Anticonvulsant	+	++	Wallace (42), Carlini (40)
Muscle relaxant	++	+	Collin (61)
Antinociceptive	++	+	Pertwee (13)
Psychotropic	++	-	Russo (108)
Anxiolytic	±	++	Zuardi (109)
Antipsychotic	-	++	Zuardi (17), Moreira (78)
Neuroprotective antioxidant	+	++	Hampson (73)
Antiemetic	++	+	Parker (99)
Sedation	+	-	Nicholson (55)
Agitation (Alzheimer disease)	+	-	Volicer (79)
Tic reduction (Tourette syndrome)	+	?	Müller-Vahl (111)
Opiate withdrawal reduction	+	?	Cichewicz (91), De Vry (36)
Migraine treatment	+	+	Russo (112)
Bipolar disease	+	?	Grinspoon (113)
Dystonia		+	Consroe (85)
Parkinsonian symptoms	+	?	Venderova (51)
Withdrawal symptoms to other drugs (reduction)	+	+	Labigliani (89), Dreher (90), De Vry (36)
Motor neurone disease (ALS) (increased survival, function)	+	+	Raman (81), Abood (82)
Cardiovascular Effects			
Bradycardia	-	+	Weil (114)
Tachycardia	+	-	Karniol (33)
Hypertension	+	-	Weil (114)
Hypotension	-	+	Batkai (115)
Appetite/Gastrointestinal			
Appetite	+	-	Pertwee (14)
GI motility (slowed)	++	+	Pertwee (14)
Anti-Carcinogenesis			
Glioma (apoptosis)	+	+	Sanchez (116), Massi (117)
Glioma cell migration		+	Vaccani (98)
Ophthalmological			
Intra-ocular pressure (reduced)	++	+	Jarvinen (118)
Night vision	+	-	Russo (119)

Figure 3 Effects of tetrahydrocannabinol (THC) and cannabidiol (CBD), adapted and updated from Russo 2003 [52] ([13,14,17,20,21,33,36,40,42,51,55,61,73,78,79,81,82,85,89–91,98,99,104–109,111–119]).

ory or short-term memory, even in doses up to 50 mg/kg.

A review of human studies of THC and CBD simultaneously administered

Administration of CBD orally (up to 300 mg) and IV (up to 30 mg) in volunteers were felt to be inactive in early experiments [31], with similar conclusions after IV infusion by another group [32].

In Brazil in 1974, effects of THC up to 30 mg and CBD up to 60 mg orally were studied in varying ratios in blinded fashion in 40 male subjects [33]. CBD at doses 15—60 mg evidenced few effects of its own, but effectively countered effects of 30 mg of THC including tachycardia, disturbed time tasks and strong psychological reactions. Interestingly, with higher doses of THC (p. 175), ''symptoms appeared in 'waves' during which the subjects reported strong feelings of anxiety reaching sometime a near panic state''. (These complaints are similar to those voiced by Marinol® patients currently when the dosage is not tolerated; perhaps enterohepatic circulation is operative.) With addition of CBD, the authors observed (p. 176), ''CBD also changed the symptoms in such a way that the subjects receiving the mixtures showed less anxiety and panic but reported more pleasurable effects''. Unfortunately, this statement was interpreted in context by the anonymous author(s) of a *US Federal Register* article [34] (p. 20065) as follows, ''Most importantly, CBD appears to potentiate the euphorigenic and reinforcing effects of THC which suggests that the interaction between THC and CBD is synergistic and may actually contribute to the abuse of marijuana''. This contention is unsupported by any of the cited literature. Furthermore, as the context of the discussion pertains to smoked cannabis in the USA, it is impertinent, as North American drug strains of cannabis are virtually devoid of CBD-content [35]. No epidemiological data are evident in any of the world's literature that supports the allegation that the presence of CBD contributes or promotes cannabis abuse. In fact, the neutral antagonism of CB_1receptors by CBD should actually reduce risk of development of tolerance [36] (vide infra).

In 1975, Hollister and Gillespie [37] noted very little THC—CBD interaction clinically in humans, except for a delayed onset and prolongation of THC effects that was so slight as to be felt negligible by the authors, who actually suggested it appropriate to ignore the CBD content of test cannabis.

In a test of smoked placebo cannabis with or with THC and a sixfold higher dose of CBD [38], the 'high' of THC was significantly attenuated when CBD was present: 11/15 subjects felt the effects of THC alone as greater than the combination.

In a similar protocol [39], co-administration of smoked CBD with THC attenuated THC effects including tachycardia, impairment on stance stability on a wobble board, and ability to track on a pursuit meter.

In 1981, cannabidiol was tested as an anticonvulsant in Brazil [40]. Fifteen patients with frequent attacks of unresponsive 'secondarily generalized epilepsy' (seizures of partial onset with secondary generalisation), aged 14—49, were treated with CBD vs. placebo in double-blind fashion. Three of eight treated patients had complete seizure control with 200 mg of CBD per day, and a fourth with 300 mg per day. One was improving, but was unavailable for follow-up. One other was markedly improved, two somewhat, and one not at all. Neither laboratory changes, nor major adverse effects were noted; merely some somnolence in four subjects. The latter has been misinterpreted in much subsequent literature to support a sedative property of CBD.

As, subsequent recent work has confirmed powerful anticonvulsant effects of THC and the key role of the endocannabinoid system in regulating seizure thresholds [41,42], it is logical to think that THC:CBD combinations may produce effective anticonvulsants.

Additional clinical experimentation in normal subjects [16], THC provoked anxiety that was antagonised by concomitant CBD administration. When given alone, subjective assessments of CBD effects included such terms (p. 249) as, 'quick witted' and 'clear minded'.

Modern clinical trials of cannabis extracts containing THC and CBD

Cannador

A recent small clinical trial of THC and an oral cannabis extract (Cannador) was performed with 16 subjects. Neither was observed to reduce spasticity, and adverse events were reported as greater in the extract group even at low dosages [43]. Numerous criticisms were subsequently voiced in this regard [44] such that the plant extract was poorly categorised, and employed sub-optimal oral administration with no real dose titration. An

additional study in Switzerland [45] with more patients and doses of up to 15 mg THC with 6 mg CBD equivalent PO divided did provided better results with reduction in spasms ($p < 0.05$) and no significant side effects vs. placebo.

A British group examined 667 MS patients taking placebo, Marinol® (synthetic THC) or Cannador capsules over 15 weeks, with daily doses up to 25 mg THC equivalent (CAMS Study) [46]. While no change was seen in Ashworth Scales, improvement was observed on 10 m walking time, and subjective pain and spasticity ($p = 0.003$). Interestingly, fewer relapses were noted in the Cannador group during the study course, suggesting possible neuroprotective effects. Data from the same cohort were assessed for benefit on tremor, but no treatment benefit was observed [47]. In follow-up after one year, however, improvement was noted in spasticity for Marinol, but not Cannador [48]. In a recent review, it was suggested that this result points to THC as the active component and even that CBD detracts from therapeutic benefit [49]. Further data presented below will possibly support a different conclusion.

Cannador has also been assessed in treatment of parkinsonian dyskinesia, but without benefit in a four-week trial [50]. Better results were reported in a Czech survey study of Parkinson disease in which oral herbal cannabis with no analysis of cannabinoid content was taken for longer periods of time with improvement in multiple symptoms [51].

Cannador is an ethanolic extract that has not been particularly well characterised as to components or pharmacokinetics in published sources. Although labelled as 'standardised', clear variation in cannabinoid content has been reported in available studies with THC:CBD ratios noted as 2.5:0.9 [45], unspecified [43], or 2.5:1.25 = 2:1[46,50], or just 2.5 mg of THC with no mention of CBD [47]. It is supplied as oral gelatine capsules in oil.

Experience with oromucosal cannabis based medicines

Sativex® is a highly standardised medicinal product composed of liquid carbon dioxide extracts from selected strains of cloned cannabis plants cultivated employing Good Agricultural Practice (GAP), to provide high and reproducible yields of THC and CBD. Sativex is a 1:1 combination from two clonal cannabis cultivars yielding a high THC extract (Tetranabinex®) and a high CBD extract (Nabidiolex®). The dried of unfertilised female flowers are extracted and refined utilising Good Manufacturing Practice (GMP) produce a botanical drug substance (BDS) of defined composition with controlled reproducibility batch to batch. THC and CBD comprise some 70% (w/w) of the total BDS, with minor cannabinoids (5—6%), terpenoids (6—7%, most GRAS (Generally Recognized as Safe)), sterols (6%), triglycerides, alkanes, squalene, tocopherol, carotenoids and other minor components (also GRAS) derived from the plant material. BDS is formulated into a spray for oromucosal administration with each 100 μL pump-action spray providing 2.7 mg of THC and 2.5 mg of CBD, the minor components, plus ethanol:propylene glycol excipients, and 0.05% peppermint as flavouring [52].

Extensive pharmacokinetic and pharmacodynamic studies have been undertaken with the three extracts in normal volunteers. Pertinent observations comparing extracts in context include the following:

(1) The preparation has onset of activity in 15—40 min, which allows patients to titrate dosing requirements according to symptoms, with a very acceptable profile of adverse events.
(2) When CBD and THC extracts were co-administered as sublingual drops, the rate of appearance of THC in serum was marginally increased possibly suggesting a stimulation of THC absorption [53].
(3) The appearance of 11-OH—THC was reduced when CBD was co-administered with THC extracts [53].
(4) THC T_{max} was later following the 1:1 mixture as compared to high-THC possibly due to CBD delaying THC absorption [54].

Observations (2) and (4) may appear contradictory, but the findings are unlikely to have great clinical significance. While patients differed, sometimes markedly, in pharmacokinetic values, especially with respect to cannabidiol, in all instances, reliable serum levels of THC and CBD were produced via the oromucosal route.

In a Phase I study of sleep and cognitive effects in eight normal volunteers [55], the THC:CBD 1:1 combination produced less sedation than THC-predominant extract and rather, some alerting properties. Although memory impairment was noted the following day after 15 mg THC extract, none was apparent with concomitant administration of CBD. The 1:1 mixture produced therapeutic advantages over effects seen with single components, as CBD counteracted residual effects of THC on daytime sleep latencies and memory.

In a subsequent Phase II clinical trial in 20 patients with intractable neurogenic symptoms [56], significant improvements (all $p < 0.05$) were seen as follows: THC- and CBD-predominant extracts on pain (especially neuropathic), THC- and 1:1 extracts on spasm, THC extract on spasticity, THC extract on appetite, and 1:1 extract on sleep. Post-hoc analysis revealed that overall symptom control was best with THC:CBD 1:1 ($p < 0.0001$), and in a subset of patients with MS ($p < 0.0002$), and intoxication was less than with THC-predominant extract.

In another Phase II study of intractable chronic pain [57], in 24 subjects who did not employ rescue medication, visual analogue scales (VAS) were 5.9 for placebo, 5.45 for CBD, 4.63 for THC and 4.4 for 1:1 THC:CBD extracts ($p < 0.001$). Sleep was also most improved on the latter ($p < 0.001$). Of 28 subjects, 11 preferred THC:CBD overall, while 14 found THC and THC:CBD equally satisfactory. Once more, for pain in the MS patients, THC:CBD produced best results ($p < 0.0042$).

In a Phase II, open label study of THC-predominant and 1:1 THC:CBD extracts vs. placebo in patients with intractable lower urinary tract symptoms, both active groups had significant improvement in urgency, cumber and volume of incontinence episodes, frequency, nocturia, daily total void volume, catheterised and urinary incontinence pad weights [58].

Once again, in a Phase III study of intractable pain associated with brachial plexus injury [59], roughly equivalent benefits were noted in Box Scale-11 pain scores with THC-predominant ($p = 0.002$) and THC:CBD 1:1 extracts ($p = 0.005$).

On the basis of these results with oromucosal cannabis based medicines, Professor Carlini has stated [60] (p. 463), 'However, any possible doubts that might exist on whether or not Δ^9-THC is an useful medicine for MS symptoms, were removed by the results obtained in four very recent randomized, double-blind, placebo-controlled trials'.

In a study of 189 subjects with clinically definite MS with associated spasticity from 12 European centres, patients were randomised 2:1 to receive self-titrated daily doses of THC:CBD 1:1 ($N = 124$) or placebo ($N = 65$) in a double blind trial of eight weeks duration [61]. The THC:CBD oromucosal cannabis based medicine produced statistically significant objective benefit on spasticity on Motricity Index of lower extremities, as well as subjective improvement in NRS measures of spasticity, and responder analysis with a very acceptable adverse event profile compared to placebo.

In a controlled double-blind clinical trial of intractable central neuropathic pain [62], 66 MS subjects showed mean Numerical Rating Scale (NRS) analgesia favouring THC:CBD 1:1 extract over placebo ($p = 0.009$), with sleep disturbances scores also positive ($p = 0.003$). There were no major changes in neuropsychological test measures vs. placebo. In marked contrast, results in two articles examining Marinol in central or peripheral neuropathic pain with oral doses up to 25 mg revealed no clear benefit on pain or allodynia, and with poor tolerance to adverse events [63,64]. A study of two subjects with similar doses for 2—5 years showed initial decrements in pain, but with unsustained temporal improvement [65]. Better results were seen in a Swedish study [66], limiting Marinol doses to 10 mg/d in 24 subjects with central neuropathic pain due to MS. Median numerical pain scale in final week favoured Marinol ($p = 0.02$), as did median pain relief ($p = 0.035$). Authors rated analgesic effect as 'modest'. While number needed to treat (NNT) to attain a 30% decrement in pain were comparable in this study vs. Sativex, the reduction of pain on a numerical rating scale favoured the latter (1.0 vs. 0.6), as did side effect profile particularly for somnolence and headache, despite much higher total doses of THC and the concomitant usage of additional medicines for neuropathic pain. These differences point to either an advantage of oromucosal administration of phytocannabinoids, a reduction of THC adverse events due to inclusion of CBD, or both.

In a Phase III, double-blind placebo-controlled trial of peripheral neuropathic pain characterised by allodynia [67], THC:CBD 1:1 produced highly statistically significant improvements in pain levels with additional benefit on static and dynamic allodynia measures.

In a Phase III, double-blind placebo-controlled trial in 160 subjects with various symptoms of MS [68], THC:CBD 1:1 significantly reduced spasticity over placebo ($p = 0.001$) without significant adverse effects on mood or cognition. In a long-term safety-extension study (SAFEX), some 137 patients elected to continue on THC:CBD 1:1 [69]. On VAS of symptoms, rapid declines were noted over the first 12 weeks in pain ($n = 47$), spasm ($n = 54$), spasticity ($n = 66$), bladder problems ($n = 57$), and tremor ($n = 35$), with slower sustained improvements for more than one year. Interestingly, no tolerance was noted with mean THC:CBD 1:1 doses actually declining over time. Furthermore, VAS of intoxication in the cohort measured in the single digits out of 100 and did not differ significantly from placebo. In a cohort of 18 volunteers who abruptly stopped THC:CBD 1:1, no significant evidence for a withdrawal syndrome was observed. Rather, patients suffered recrudescence of symptoms after 7—10

days, but easily re-titrated to prior dosages with renewed efficacy.

Finally, the recently announced results of a Phase III study comparing THC:CBD 1:1, THC-predominant extract and placebo in intractable pain due to cancer unresponsive to opiates [70] with strong neuropathic pain components, demonstrated that THC:CBD 1:1 produced highly statistically significant improvements in analgesia ($p = 0.0142$), while the THC-predominant extract failed to do so in this trial, confirming the key importance of the inclusion of CBD in the preparation.

Analysis of sleep parameters in seven Phase II and III trials of MS and neuropathic pain and two corresponding SAFEX studies to date demonstrate significant to highly statistically significant and durable benefits of THC:CBD 1:1 on this important clinical symptom [71].

These trials, combined with their safety-extension studies comprise some 1500 subjects and 1000 patient-years of experience, during which no abuse or diversion of THC:CBD 1:1 have occurred, and no tolerance or withdrawal effects have been noted [69,72]. Thus, the fears expressed in the *Federal Register* [34] with respect to CBD—THC interactions appear unfounded.

New horizons in phytocannabinoid therapeutics

Neuroprotection

The seminal work describing the neuroprotective roles of THC and CBD has been that of Hampson et al. [73]. Both phytocannabinoids protected equally against glutamatergic neurotoxicity mediated by NMDA, AMPA, or kainate receptors, and this effect was not antagonized by SR1414716A, thus demonstrating it to be operative independently of cannabinoid receptor activation. The group additionally investigated the effects of THC and CBD on reactive oxygen species (ROS), finding them equal to that of the BHT and HU-211 (dexanabinol). CBD was considerably more potent as an antioxidant than ascorbate or tocopherol. Recent work has also shown that CBD reversed binge ethanol-induced neurotoxicity via a cannabinoid receptor-independent antioxidant mechanism [74], and prevented cerebral infarction via a 5-HT_{1A} receptor dependent mechanism [75]. Activity of CBD at that receptor has been independently confirmed [76], supporting a role in migraine and anxiety treatment.

Cannabidiol was shown to prevent β-amyloid induced toxicity in the PC12 phaeochromocytoma model of Alzheimer disease [77], increasing cell survival, while decreasing reactive oxygen species (ROS) production, lipid peroxidation, caspase 3 levels, DNA fragmentation and intracellular calcium.

A recent study [78] in mice supports the prospect that CBD has antipsychotic properties without extrapyramidal side-effects. Thus, CBD might improve symptoms of agitation and behavioural issues previously treated to advantage with THC alone in a clinical Alzheimer population [79].

One article has described the palliative use of cannabis in motor neurone disease, or amyotrophic lateral sclerosis (ALS) [80]. THC has previously been shown to delay motor deterioration and increase survival in a mouse model of ALS [81]. That work was recently extended to demonstrate that the addition of CBD further slowed disease progression with a 14% improvement in motor performance, and a trend toward extension of survival beyond that previously achieved with THC alone [82].

The intriguing survey supporting symptomatic improvement in Parkinson disease (PD) after prolonged usage was previously mentioned [51]. This finding is lent additional credence by the demonstration that equivalent benefits were observed with THC and CBD in preventing damage produced by injection of 6-hydroxydopamine into the median forebrain bundle of experimental animals [84], a result independent of cannabinoid receptor effects, but more likely due to antioxidant activity and regulation of glial influences upon neurones. This would support a neuroprotective benefit beyond the issue of symptomatic relief that would warrant additional trials, particularly with a mixed THC:CBD preparation.

Dystonic disorders are frequently progressive degenerative diseases, wherein CBD was employed in isolation and demonstrated benefit [85].

CBD treatment was attempted in Huntington's disease [86], but with little benefit seen over the 6-week trial. Perhaps the length of treatment was too short, and may support the concept of additional trials, particularly with a THC:CBD preparation. Such a combination may well prove to effect neuroprotective benefits in MS in the long term, having a strong theoretical basis [87]. Given the failure of various glutamate antagonists in efforts at neuroprotection in this and other conditions, phytocannabinoid approaches certainly appear warranted.

Cannabinoids and dependency

A simple perusal of the medical literature will confirm that considerable concern continues in

context as to the drug abuse liability of THC preparations. However, that substance in isolation has proven to pose little risk [12]. To the extent that rapidly rising serum levels promote reward and addictive potential of a given pharmaceutical [88], it is certainly arguable that the addition of CBD to THC would reduce psychoactive attraction, and that an oromucosal delivery eliminates the steep slope pharmacokinetic profile of cannabis smoking [54]. Additionally, cannabinoid receptor blockade by CBD may well reduce addiction potential [36], and support its usage as an 'anti-addictive' compound [72]. Interestingly, THC and CBD have both been demonstrated to potentiate the extinction of cocaine and amphetamine conditioned incentive learning in rats, supporting clinical studies claiming benefit of cannabis on cocaine addiction in Brazil [89] and Jamaica [90].

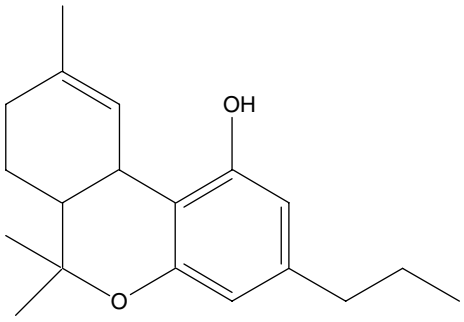
The fact that THC potentiates opiate analgesia, eliminates morphine tolerance and reduces withdrawal [91] highlights the rationale of cannabinoid–opiate combinations for treatment of severe and chronic pain. Recently, it was shown that interleukin-1 (IL-1) antagonises morphine and underlies development of tolerance [92]. As THC and CBD both suppress IL-1 secretion in humans in mononuclear cells in vitro [93], it is possible that this mechanism may also play a helpful role in addiction issues with a combined pharmaceutical.

Neoplastic disease

THC has demonstrated cytotoxic benefits and anti-angiogenic effects in a wide variety of cell lines (reviewed in [94,95]). CBD has also proven active as a cytostatic/cytotoxic, especially in gliomas where it inhibits cell migration leading to tumour invasion [96], decreases oxidative mitochondrial metabolism with decrease in cell survival and inducing apoptosis in vitro and in vivo [97], and additionally inhibits cell migration, underlying metastatic mechanisms, independently of CB_1 and CB_2 [98]. Given the analgesic effect of the THC:CBD combination in cancer treatment discussed above [70], the side benefit of THC and CBD [99] in chemotherapy-associated nausea, and these primary effects on tumour growth and spread, a strong rationale is currently present for their application in additional clinical trials.

Conclusion

Various publications have presented the position that THC accounts for the main effects [100], the analgesic and other medicinal benefits [101] of cannabis. This paper supports a distinct view that CBD and perhaps other cannabis components [6] achieve synergy with THC [102] consisting of potentiation of benefits, antagonism of adverse effects, summation (à *la* the entourage effect), pharmacokinetic advantages (in CBD suppression of 11-hydroxylation of THC), and metabolism (e.g., lower toxicity of a 'natural product' as compared to synthetic COX-inhibitor anti-inflammatory). The range of effects of the phytocannabinoids on pathophysiological processes is truly impressive, and suggests broad applicability in their future therapeutic application.



tetrahydrocannabivarin

Figure 4 Tetrahdrocannabivarin (THCV), a propyl phytocannabinoids with potent antagonist properties at CB_1 [103].

The recent discovery that the propyl phytocannabinoid, tetrahydrocannabivarin (THCV) (Fig. 4), is a potent antagonist at the CB1 receptor [103] supports the notion that we yet have a great deal to learn about the therapeutic potential of this venerable medicinal plant.

The data herein presented strongly support the therapeutic rationale for combining THC and CBD for therapeutic usage.

Conflict of interest/role of funding Source

The author has been a consultant for GW Pharmaceuticals since 1998, and has received grants-in-aid, travel expenses, research support, stock options and salary in this regard.

Search strategy and selection criteria

References for this review were identified by searches of PubMed/National Library of Medicine

database from 1966 to June 2005 for articles pertinent to cannabidiol and its combination with THC in English, French, Spanish, Portuguese and Italian. Additional sources were identified in the author's extensive personal library of books and files.

Acknowledgements

The author thank Richard Musty for suggesting certain references and Emma Brierley and Alice Mead for suggested revisions.

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