

Clinical Endocannabinoid Deficiency (CECD): Can this Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and other Treatment-Resistant Conditions?

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Abstract

OBJECTIVES: This study examines the concept of clinical endocannabinoid deficiency (CECD), and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis.

METHODS: Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other resources.

RESULTS: Migraine has numerous relationships to endocannabinoid function. Anandamide (AEA) potentiates 5-HT_{1A} and inhibits 5-HT_{2A} receptors supporting therapeutic efficacy in acute and preventive migraine treatment. Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. AEA is tonically active in the periaqueductal gray matter, a migraine generator. THC modulates glutamatergic neurotransmission via NMDA receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, IBS and related disorders. The past and potential clinical utility of cannabis-based medicines in their treatment is discussed, as are further suggestions for experimental investigation of CECD via CSF examination and neuro-imaging.

CONCLUSION: Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines.

Abbreviations

AEA:	arachidonylethanolamide, anandamide
2-AG:	2-arachidonylglycerol
CB ₁ :	cannabinoid 1 receptor
CBD:	cannabidiol
CECD:	clinical endocannabinoid deficiency
CGRP:	calcitonin gene-related peptide
CNS:	central nervous system
CRP:	complex regional pain
ECT:	electroconvulsive therapy
FAAH:	fatty acid amide hydrolase
fMRI:	functional magnetic resonance imaging
5-HT:	5-hydroxytryptamine, serotonin
GI:	gastrointestinal
IBS:	irritable bowel syndrome
NMDA:	N-methyl-D-aspartate
PAG:	periaqueductal gray
PET:	positron emission tomography
PTSD:	post-traumatic stress disorder
RSD:	reflex sympathetic dystrophy
THC:	Δ^9 -tetrahydrocannabinol
TMJ:	temporomandibular joint
VR ₁ :	vanilloid 1 receptor

Introduction

In the initial lines of his 1895 work, *Project for a Scientific Psychology*, Sigmund Freud stated [1] (p. 295), "The intention is to furnish a psychology that shall be a natural science: that is, to represent psychical processes as quantitatively determinate states of specifiable material particles, thus making those processes perspicuous and free from contradiction." Freud was frustrated in this effort, and found that available science at the twilight of the 19th century was not capable of providing biochemical explanations for cerebral processes, leading him to pursue psychodynamic theory alternatively.

At the dawn of the 21st century, despite astounding progress in psychopharmacology, medicine remains challenged in its attempts to understand and successfully treat a large number of recalcitrant syndromes, noteworthy among them, migraine, fibromyalgia, and irritable bowel syndrome (IBS). For many physicians these problematic entities suggest a psychosomatic or "functional" etiology that remains shorthand for a diagnosis where our biochemical understanding and therapeutic vigor fall short of the mark.

In the last fifteen years, however, the discovery of the endogenous cannabinoid (endocannabinoid) system [2] has provided new insights into a neuro-modulatory scheme that portends to provide better explanations of, and treatments for, a wide variety of previously intractable disorders, particularly painful conditions (reviewed in [3; 4]).

After all, for each neurotransmitter system there are pathological conditions attributable to its deficiency: dementia in Alzheimer disease due to loss of acetylcholine activity, Parkinsonism due to dopamine deficiency, depression secondary to lowered levels of serotonin, norepinephrine or other amines, etc. Should the situation be any different for the endocannabinoid system, whose receptor density is in fact greater than many of the others? This article will explore that question and propose a concept first articulated in prior

publications [5; 6], that a clinical endocannabinoid deficiency (CECD), whether congenital or acquired may help to explain the pathophysiology of certain diagnostic pitfalls, especially those characterized by hyperalgesia, and thereby provide a basis for their treatment with cannabinoid medicines.

Mechanisms of action of cannabis and THC have recently been elucidated with the discovery of cannabinoid receptors and an endogenous ligand, arachidonylethanolamide, nicknamed anandamide, from the Sanskrit word *ananda*, or "bliss" [7]. Anandamide (AEA) inhibits cyclic AMP mediated through G-protein coupling in target cells, which cluster in nociceptive areas of the CNS [8]. Preliminary tests of its pharmacological action and behavioral activity support similarity of AEA to THC [9], and both entities are partial agonists at the CB₁ receptor. Pertwee [4] has examined the pharmacology of cannabinoid receptors and pain in detail.

Methods

Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other Internet resources.

Results*Migraine*

Migraine is a public health issue of astounding societal cost. There are an estimated 23 million sufferers in the USA [10], with an economic impact of \$1.2 to \$17.2 billion annually [11]. The neurochemistry of migraine is among the most complex of any human malady, and its relation to cannabinoid mechanisms has been examined previously in brief [12] and in depth [5].

Serotonergic pathways are considered integral to migraine pathogenesis and treatment. Numerous points of intersection with cannabinoid mechanisms are evident: THC inhibits serotonin release from the platelets of human migraineurs [13]; THC stimulates 5-HT synthesis, inhibits synaptosomal uptake, and promotes its release [14]; AEA and CB₁ agonists inhibit rat serotonin type 3 (5-HT₃) receptors [15] involved in emetic and pain responses. Additionally, AEA produces an 89% relative potentiation of the 5-HT_{1A} receptor response, and a 36% inhibition of the 5-HT_{2A} receptor response [16]. Another endocannabinoid, 2-arachidonylglycerol (2-AG) inhibited 5-HT_{2A} by 28%. Recently, mild but significant similar activity on 5-HT_{2A} has been demonstrated for cannabidiol [17], and cannabis terpenoids [18]. Higher concentrations of anandamide decreased serotonin and ketanserin binding (the latter being a 5-HT_{2A} antagonist) [19]. These observations support putative efficacy of therapeutic cannabinoids in acute migraine (agonistic activity at 5-HT_{1A} or D) and in its prophylactic treatment (antagonistic activity at 5-HT_{2A}) [20].

The importance of dopaminergic mechanisms in migraine has also been explored [21]. 6-hydroxydopamine, which causes degeneration of catecholamine

terminals, blocked THC antinociception [22]. AEA stimulates nitric oxide formation through inhibition of presynaptic dopamine release [23]. Dopamine blocking and modulatory effects of cannabis and THC have been demonstrated in studies of Tourette syndrome [24; 25], and schizophrenia in Germany [26], suggesting that THC may similarly modulate dopaminergic imbalances in headache.

Inflammatory mechanisms affected by cannabis are legion (reviewed [27–31]. THC and cannabinoids inhibit prostaglandin E-2 synthesis [32]; smoked cannabis reduces platelet aggregation [33]; THC demonstrated an oral potency as an anti-inflammatory 20 times that of aspirin and twice that of hydrocortisone [34], and cannabidiol (CBD) inhibited both cyclooxygenase and lipoxygenase. Similarly, anandamide and metabolites are substrates for brain lipoxygenase [35]. Opiates, cannabinoids and eicosanoids signal through common nitric acid coupling [36], while THC blocks the conversion of arachidonate into metabolites derived by cyclooxygenase activity, and stimulates lipoxygenase, promoting down-regulation of inflammation.

CNS beta-endorphin levels are depleted during migraine attacks [37], but THC experimentally increases them [38]. THC additionally regulates substance P and enkephalin mRNA levels in the basal ganglia [39]. THC affects an analgesic brainstem circuit in the rostral ventromedial medulla that interacts with opiate pathways [40], mediating antinociception after activation of neurons in the midbrain periaqueductal grey matter (PAG), a putative migraine generator area [41], wherein THC and other cannabinoids are antinociceptive [42]. The PAG is an integral processor of ascending and descending pain pathways, fear and anxiety [43]. Additional support is provided by studies demonstrating tritiated sumatriptan binding in human PAG [44], and that THC administration elevates proenkephalin gene expression in the PAG [45]. Most compelling is data supporting tonic activity of anandamide in the PAG with production of analgesia, and hyperalgesia upon cannabinoid antagonism [46].

Cannabinoids may represent a therapeutic advantage over opiates, particularly in treatment of neuropathic pain [47]. Opiates commonly aggravate migraine or even provoke its appearance [48], as observed therapeutic doses of morphine failed to alleviate acute attack and increased hyperalgesia in migraineurs during inter-ictal periods.

A trigeminovascular system has long been implicated as integral to the pain, inflammation and secondary vascular effects of migraine, linked through the NMDA/glutamate system [49]. Cannabinoid agonists inhibit voltage-gated calcium channels, and activate potassium channels to produce presynaptic inhibition of glutamate release [50], without dissociative effects noted with other NMDA inhibitors, such as ketamine. Subsequently, THC was shown to modulate glutamatergic transmission through a reduction without blockade [51]. NMDA antagonism was felt to be effective in eliminating hyperalgesia associated with migraine [52], as well a “secondary hyperalge-

sia” with exaggerated responses to noxious stimuli in areas adjacent to the pain. NMDA blockade was recommended to treat chronic daily headache [53]. This group also addressed how a genetic predisposition (“third hyperalgesia”) may lead to a “chronicization” of migraine through NMDA stimulation [54].

THC and CBD phytocannabinoids also act as neuroprotective antioxidants against glutamate neurotoxicity and cell death mediated via NMDA, AMPA and kainate receptors [55], independently of cannabinoid receptors, and exceed the antioxidant potency of vitamins C and E.

Migraine is a complex neurochemical disorder with myriad effects beyond pain. Its tendency to produce photophobia and phonophobia, even between discreet attacks [56], may be considered suggestive of a “sensory hyperalgesia,” as these normally tolerated sensations take on painful proportions.

The combination of endocannabinoids and their inactive precursors have been dubbed an entourage effect [57], and an analogous synergy of phytocannabinoids, cannabis terpenoids and flavonoids has also been suggested and analyzed at some length [58]. The unique attributes of cannabis to affect serotonergic, dopaminergic, opioid, anti-inflammatory, and NMDA mechanisms of migraine, both acutely and prophylactically, have rendered it a proposed “ideal drug” for its treatment [5].

Migraine is a strongly genetic disorder, but similar symptoms are acquired under conditions of closed head injury, where the “post-traumatic syndrome” displays similar symptoms. A protective role of endocannabinoids in such settings is evident in the findings that 2-AG is elevated after experimental brain injury, and that it plays an important neuroprotective role [59].

Unfortunately, no organized clinical trials of cannabis in migraine have been performed. While documentation of the use of cannabis for migraine suggests a 4000 year history, and it was a major indication for cannabis medicines in Western society between 1842 and 1942 [5], there have been few modern studies beyond the “anecdotal” [5; 60–62]. Surveys in California indicate that of 2480 patients served by the Oakland Cannabis Buyers’ Club, 127, or 5%, sought cannabis for treatment of chronic migraines [63]. Success rates of some 80% with North American strains of cannabis have been estimated based on clinical contact [5]. Experience in prophylactic use of Marinol® (synthetic THC) in some ten patients was disappointing, with some decrement in frequency and severity of attacks, but not total remission or “cures” claimed by 19th century authors with extracts of Indian hemp [5]. The difference may well be due to a nearly total dearth of cannabidiol in North American cannabis strains [64] (see discussion below), and the observed possibility of CBD modulation of serotonergic function [17]. More formal documentation of clinical efficacy would be distinctly welcome.

Fibromyalgia

Fibromyalgia, or myofascial pain syndrome, is an extremely common but controversial condition, whose very basis has been questioned, particularly among neurologists [65]. Even this author must admit to past prejudice in labeling it a “semi-mythical pseudo-disease.” Notwithstanding these opinions, the condition is the most frequent diagnosis in American rheumatology practices. Bennett has provided an excellent review [66], emphasizing new insights into fibromyalgia as a condition indicative of “central sensitization” and amplification of somatic nociception. While no clear chemical or anatomical pathology has been clarified in tender muscle points, these present a self-sustaining and amplifying influence on pain perception in the brain over time, and lead to a concomitant disturbances in restful sleep, manifestations of dysautonomia, and prevalent secondary depression. Interestingly, the application of standard antidepressant medication to the latter, and pharmacotherapy in general, provide disappointing results in fibromyalgia treatment. Has a promising therapeutic avenue been missed?

Returning to the work of Nicolodi and Sicuteri, the “secondary hyperalgesia” manifested by an increased response to noxious stimuli in areas adjacent to the pain is common to migraine and fibromyalgia (see below). These authors suggested NMDA blockade as an approach to pain in defects of serotonergic analgesia in fibromyalgia [67].

Several studies of Richardson and her group provide key support for a relation of fibromyalgia and similar conditions to a clinical endocannabinoid deficiency. An initial study [68] demonstrated that intrathecal injection of SR141716A, a powerful cannabinoid antagonist/inverse agonist, resulted in thermal hyperalgesia in mice. This suggests that the endocannabinoid system regulates nociceptive thresholds, and that absence of such regulation, or endocannabinoid hypofunction, underlies hyperalgesia and related chronic pain conditions. In a subsequent study [69], oligonucleotides directed against CB₁ mRNA produced significant hyperalgesia. Additionally, the hyperalgesic effect of SR141716A was blocked in a dose-dependent manner by co-administration of two NMDA receptor antagonists, again supporting tonic activity of the endocannabinoid system under normal conditions. On this basis, it was suggested that cannabinoid agonists would be applicable to treatment of chronic pain conditions unresponsive to opioid analgesics.

Further investigation demonstrated that intrathecal AEA totally blocked carrageenan-induced spinal thermal hyperalgesia, while having no effect on normal thermal sensory and antinociceptive thresholds [70]. Additionally, AEA inhibited K⁺ and capsaicin-evoked calcitonin gene-related peptide (CGRP) release, and CB₁ receptors were identified in rat sensory neurons and trigeminal ganglion. On this basis, the authors recommended cannabinoids for disorders driven by a primary afferent barrage (e.g., allodynia,

visceral hyperalgesia, temporomandibular joint pain (TMJ), and reflex sympathetic dystrophy (RSD)), and that such treatment could be effective at sub-psychoactive dosages.

Another study examined peripheral mechanisms [71], wherein AEA acted on CB₁ to reduce hyperalgesia and inflammation via inhibition of CGRP neurosecretion in capsaicin activated nerve terminals. This is akin to mechanisms of “sterile inflammation” observed centrally in migraine, where CGRP is felt to be an important mediator [5]. Overall the results supported the notion that endocannabinoids modulate neurogenic inflammation through inhibition of peripheral terminal neurosecretion in capsaicin-sensitive fibers. AEA demonstrated anti-edema effects in addition to anti-hyperalgesia. Similar implications were provided by another study [72], in which WIN 55,212-2, a powerful CB₁ agonist, blocked capsaicin-induced hyperalgesia in rat paws. Once more, the benefit occurred at a dosage that did not produce analgesia or motor impairment, suggesting therapeutic benefit of cannabinoids without adverse effects. Similarly, local THC administration was evaluated in capsaicin-induced pain in rhesus monkeys [73], where, once more, pain was effectively reduced at low dosage, and was blocked by a CB₁ antagonist.

Another concept that is important to understanding of fibromyalgia is “wind-up,” a central sensitization of posterior horn neurons in pain pathways that occurs secondarily to tonic impulses from nociceptive afferent C fibers dependent on NMDA and substance P synaptic mechanisms in the spinal cord [74]. Similar mechanisms were implicated in TMJ dysfunction and RSD/CRP syndromes. The authors felt that some unknown peripheral tonic mechanism maintains allodynia, hyperalgesia, central sensitization and enhanced wind-up. Unfortunately, an obvious explanation was overlooked. In a previous publication [75], it was demonstrated that wind-up was decreased in dose-dependent fashion by WIN 55,212 in spinal wide dynamic range and nociceptive-specific neurons. Thus, cannabinoids were able to suppress facilitation of spinal responses after repetitive noxious stimuli without impairment of non-nociceptive functions.

On a practical level, once more there have been no formal clinical trials of cannabis or THC in treatment of fibromyalgia. However, 21 California patients listed fibromyalgia and 11 myofascial pain (1.3% of a clinical population of 2480 subjects) as primary diagnoses leading to their usage of clinical cannabis [63]. Anecdotal reports to this author and other clinicians support unique efficacy of cannabis beyond conventional pharmacotherapy for alleviation of pain, dysphoria and sleep disturbances.

Irritable Bowel Syndrome (IBS)

IBS is another difficult clinical syndrome for patients and their physicians. It is characterized by fluctuating symptoms of gastrointestinal pain, spasm, distention, and varying degrees of constipation or especially diarrhea. These may be triggered by infection,

but dietary indiscretions also figure prominently in discrete attacks. Although many clinicians regard it as a “diagnostic wastebasket,” irritable bowel syndrome represents the most frequent referral diagnosis for American gastroenterologists. Once more, a wide variety of treatments including atropinic agents, antidepressants and others affecting a myriad of neurotransmitter systems are prescribed, often with inadequate clinical benefits.

That endocannabinoids are important in GI function was powerfully underlined by the fact that 2-arachidonylglycerol (2-AG) was first isolated in canine gut [76].

In a recent review [77], the concept of “functional” bowel disorders as disturbances displaying “visceral hypersensitivity” was emphasized, involving a veritable symphony of neuroactive and pro-inflammatory modulators. In the susceptible subject, these lead to gastrointestinal allodynia and hyperalgesia to stimuli that would not discomfit the unaffected individual. The role of vanilloid mechanisms in IBS was also explored, and it is worth emphasizing that anandamide is an endogenous agonist at VR₁ receptors, as is the phytocannabinoid cannabidiol (CBD) [78]. Repetitive VR₁ stimulation rapidly produces a sensory neuron refractory state that would be a clinical advantage in treatment of visceral hypersensitivity.

Pertwee has examined the relationship of cannabinoids to gastrointestinal function in depth [79]. To summarize: The enteric nervous systems of mammals express CB₁ and stimulation depresses gastrointestinal motility, especially through inhibition of contractile neurotransmitter release. Observed effects include delayed gastric emptying, some decrease in peptic acid production, and slowed enteric motility, inhibition of stimulated acetylcholine release, peristalsis, and both cholinergic and non-adrenergic non-cholinergic (NANC) contractions of smooth muscle, whether circular or longitudinal. These effects are mediated at the brain level as well as in the GI tract (This supports a chestnut frequently invoked by this author, “The brain and the gut speak the same language.”). These effects are opposed by CB₁ antagonists (e.g., SR141716A). This would strongly support the notion that GI motility is under tonic control of the endocannabinoid system. The latter concept was reinforced by additional investigation from the same laboratory [80], in which it was demonstrated that the virtually all of the immunoreactive myenteric neurons in the ganglia of rat and guinea pig expressed CB₁ receptors, and that there was a close correlation of such receptors to fibers labeled for synaptic protein, suggesting a fundamental role in neurotransmitter release. Additionally, it has been shown that chronic intestinal inflammation results in an up-regulation or sensitization of cannabinoid receptors [81]. CBD has little effect on intestinal motility on its own, but synergizes the effect of THC in slowing transit of a charcoal meal when used in concert [82].

In the basis of available data, Di Carlo and Izzo recommended the application of cannabinoid drugs in treatment of IBS in humans [83]. To date, those

studies have not eventuated, but cannabis has a long history in treating cholera, intestinal colic and related disorders (reviewed in [84]), and cannabis figures prominently in IBS treatment in testimonials on the Internet. Though anecdotal, reports suggest unique efficacy of symptomatic relief at cannabis dosages that do not impair activities of daily living. In comparison, recent trends in pharmacotherapy provide interesting contrasts. Alosetron, a 5-HT₃ receptor antagonist marketed for females with diarrhea-predominant IBS produces only a 12–17% therapeutic gain [85], and was temporarily removed from the American market due to fatal cases of ischemic colitis with attendant obstipation. Tegaserod, a 5-HT₄ receptor agonist marketed to women with constipation-predominant IBS, is reportedly well tolerated, but provides only a 5–15% improvement over placebo [85]. This “push-pull” dichotomy of serotonergic function in IBS is strongly suggestive that such efforts are barking up the wrong neurotransmitter tree. Rational analysis suggests that endocannabinoids may well be the more likely therapeutic neuromodulatory target, and that phytocannabinoid treatment might represent a more efficacious and safer therapeutic approach. In particularly severe IBS cases, the employment of a foaming rectal preparation of a whole cannabis extract might be considered.

Comorbidities of Migraine, Fibromyalgia and Irritable Bowel Syndrome

Further examination of pertinent literature supports that there are very interesting relationships between migraine, fibromyalgia and IBS. Recently, a syndrome of cutaneous allodynia associated with migraine has been reported [86], and experimentally, repetitive noxious stimulation of the skin in migraineurs between attacks facilitates pain perception [87]. Nicolodi, Sicuteri et al. similarly noted a decreased pain threshold in migraineurs tested with over-distension of upper extremity veins, but not mere pressure from a sphygmomanometer cuff [88], meriting a label for migraine as a “visceral systemic sensory disorder.” The same team noted a baseline fragility of serotonergic systems in migraine and fibromyalgia [89], plus the co-occurrence of primary headache in 97% of 201 fibromyalgia patients. In a later study [67], they supported the concept that both disorders represented a failure of serotonergic analgesia and NMDA-mediated neuronal plasticity. Other observations included the induction of fibromyalgic symptoms by the drug fenclonine in migraineurs but not others, and the production of migraine *de novo* in fibromyalgia patients without prior history after administration of nitroglycerine 0.6 mg sublingually. Similarly, an American group [90] examined 101 patients with the transformed migraine form of chronic daily headache, and were able to diagnose 35.6% as having comorbid fibromyalgia. Similarly, a high lifetime prevalence of migraine, IBS, depression and panic disorder were observed in 33 women meeting American College of Rheumatology criteria of fibromyalgia [91].

Sperber et al. examined separate groups of IBS and fibromyalgia patients [92]. Of the IBS cohort, 31.6% had fibromyalgia with significant numbers of tender muscle points compared to controls. Similarly, 32% of fibromyalgia patients met diagnostic criteria of IBS. In addition to these correlations, Bennett added irritable bladder syndrome to the comorbidities of fibromyalgia [66], supporting a concomitant visceral hyperalgesia [93; 94] in a condition where cannabis extracts have already proven efficacious [95].

Most recently, in an experimental protocol, it was demonstrated that IBS patients displayed cutaneous hyperalgesia that was suppressed by temporary rectal anesthesia with lidocaine [96], indicating central sensitization.

Broadening the Concept of Clinical Endocannabinoid Deficiency

One may quickly see that certain patients display symptoms of all three disorders, or additional ones considered "functional." With accrual of sufficient numbers of complaints lacking objective medical support, one assigns the label of somatization disorder. Given the above data, however, one might reasonably ask three questions in such contexts: 1) Are there as yet unelucidated biochemical explanations for these disorders? 2) Might endocannabinoid deficiency explain their pathophysiology? 3) Are the symptoms alleviated by clinical cannabis?

Globus hystericus and similar symptoms are frequently relegated to the psychogenic realm, but as a spasmodic disorder, it may well represent an endocannabinoid deficiency (CECD), as muscle tone (and tremor associated with demyelination) have been demonstrated to be under tonic endocannabinoid control in experimental animals [97]. Cannabis extracts have already proven efficacious in treatment of spasticity [98; 99].

Similarly, premature ejaculation in men is conventionally perceived as "psychological." This seems less tenable, when anecdotes support that cannabis prolongs latency, and proof is apparent in the dose responsive delay in ejaculation in rats noted in experiments with HU 210, a powerful CB₁ agonist [100].

A more obvious set of correlating conditions would be those of causalgia, allodynia and phantom limb pain, where application of cannabis based medicine extracts has already proven medically effective [99; 101]. Perhaps it will be demonstrable in the future that such conditions are associated with focal or spinal CECD states.

It has long been known that cannabinoids lower intraocular pressure in glaucoma (reviewed [102]), but only recently noted that that the mechanism is under tonic endocannabinoid control. Glaucoma also represents a vascular retinopathy for which cannabis may be neuroprotective. Perhaps an endocannabinoid deficiency is operative here as well.

Cannabis has had numerous historical applications to obstetrics and gynecology (reviewed [103]). This suggests usage of cannabinoid treatment in spasmodic

dysmenorrhea, hyperemesis gravidarum, and regulation of the uterine milieu in fertilization and unexplained fetal wastage, where endocannabinoid mechanisms have been demonstrated or implicated. Further investigation may shed light on whether dysregulation of the system underlies their pathophysiology.

In the pediatric realm, the entity of infantile colic has remained enigmatic. This disturbing anomaly is associated with apparent visceral sensitivity and distinct dysphoria, and is frequently medically recalcitrant to even desperate treatment measures with medications with serious adverse effect profiles. This author posits this to be another developmental endocannabinoid deficiency state that is likely amenable to phytocannabinoid treatment.

Endocannabinoid mechanisms also regulate bronchial function [104], and therapeutic efficacy in asthma treatment with cannabis preparations has been long known [105]. Based on similar analyses of the multi-organ involvement of cystic fibrosis [106], Fridericci has proposed endocannabinoid deficiencies as underlying the pathophysiology of that disorder, and its treatment with phytocannabinoids.

In the psychiatric realm, bipolar disorder has been therapeutically recalcitrant to high dose antidepressants, but anecdotal data support cannabis efficacy [107]. Whether endocannabinoid tone is too low in the disorder would be conjectural at this time, but in the instance of post-traumatic stress disorder (PTSD), such a foundation seems likely, as endocannabinoids have been demonstrated as essential to the extinction of aversive memories in experimental animals [108].

Recent work by Wallace et al. has also demonstrated that convulsive thresholds are also under endocannabinoid control [109; 110], and that THC prevents 100% of subsequent seizures, far in excess of the capabilities of phenobarbital and phenytoin. Affected rats demonstrated both acute increases in endocannabinoid production and a long-term up-regulation of CB₁ production as apparent compensatory effects counteracting glutamate excitotoxicity. Based on this, one might conjecture that similar changes accrue when seizures are employed therapeutically as electroconvulsive therapy (ECT), in treatment of intractable depression. It seems that the resultant memory loss and prolonged improvement in mood may well be attributable to an increase in endocannabinoid levels rectifying their previous inadequacy.

Recent theory on depression suggests that mere deficiencies of serotonin and norepinephrine may be insufficient explanations of the disorder, but rather, innate neuroplasticity is inherently impaired and requires specific treatment [111]. Cannabinoids certainly seem to enhance that plasticity with their neuroprotective abilities [112; 113], and should be further explored therapeutically.

The apoptotic and anti-angiogenic properties of endo- and phytocannabinoids in various cancers (reviewed [114; 115]) raise the hypothesis that certain people who are especially susceptible to malignancy may be endocannabinoid deficient.

Conclusions

Clinical Endocannabinoid Deficiency: Is It a Provable Concept?

The preceding material has pertained to conjectural and experimental evidence of a conceptual alternative biochemical explanation for certain disease manifestations, but one must ask how these would obtain? Baker et al. have described how endocannabinoids may demonstrate an impairment threshold if too high, and a range of normal function below which a deficit threshold may be crossed [112]. Syndromes of CECD may be congenital or acquired. In the former case, one could posit that genetically-susceptible individuals might produce inadequate endocannabinoids, or that their degradation is too rapid. The same conditions might be acquired in injury or infection. Unfortunately, the regulation of endocannabinoid synthesis and degradation are far from fully elucidated (reviewed [116]). While a single enzyme, anandamide synthase, catalyzes AEA production, its degradation by fatty acid amidohydrolase (FAAH), is shared with many substrates. To complicate matters, an endocannabinoid with antagonistic properties at CB₁ called virodhamine (*virodha*, Sanskrit for “opposition”) has recently been discovered [117]. Further research may shed light on these relationships.

In the meantime, a clinical agent that modifies endocannabinoid function will soon be clinically available in the form of cannabidiol. Recent research has demonstrated that although THC does not share VR₁ agonistic activity with AEA, CBD does so to a similar degree as capsaicin [78]. What is more, CBD inhibits uptake of the endocannabinoid anandamide (AEA), and weakly inhibits its hydrolysis. The presence of this component in available cannabis based medicine extracts portends to vastly extend the clinical applications and therapeutic efficacy of this re-emerging modality [118–120].

It is highly likely that additional regulatory roles for endocannabinoids will be discovered for this neuro- and immunomodulatory system. Some simple human experiments may be valuable, such as cerebrospinal fluid assay of AEA and 2-AG before and after ECT treatment. It is likely in the future that positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) for cannabinoid ligands may clarify these concepts.

This article has examined the inter-relationships of three clinical syndromes and biochemical basis in endocannabinoid function, as well as reflecting on other conditions that may display similar correlations. Only time and the scientific method will ascertain whether a new paradigm is applicable to human physiology and treatment of its derangements. Our insight into these possibilities is dependent on the contribution of one unique healing plant; for clinical cannabis has become a therapeutic compass to what modern medicine fails to cure.

REFERENCES

- Freud S. Project for a scientific psychology. Trans. Strachey J. In: The standard edition of the complete psychological works of Sigmund Freud. Vol. 1, 24 vols. London: Hogarth Press.; 1966. p. 281–343.
- Di Marzo V. ‘Endocannabinoids’ and other fatty acid derivatives with cannabimimetic properties: biochemistry and possible physiopathological relevance. *Biochim Biophys Acta* 1998; **1392**:153–175.
- Russo EB. Role of cannabis and cannabinoids in pain management. In: Weiner RS, editors. *Pain management: A practical guide for clinicians*. 6th edit., 2 vols. Boca Raton, FL: CRC Press; 2002. p. 357–375.
- Pertwee RG. Cannabinoid receptors and pain. *Prog Neurobiol* 2001; **63**:569–611.
- Russo EB. Hemp for headache: An in-depth historical and scientific review of cannabis in migraine treatment. *Journal of Cannabis Therapeutics* 2001; **1**:21–92.
- Russo EB. Handbook of psychotropic herbs: A scientific analysis of herbal remedies for psychiatric conditions. 2001. Haworth Press, Binghamton, NY.
- Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992; **258**:1946–1949.
- Herkenham MA. Localization of cannabinoid receptors in brain: relationship to motor and reward systems. In: Korman SG, Barchas JD, editors. *Biological Basis of Substance Abuse*. London: Oxford University; 1993. p. 187–200.
- Fride E, Mechoulam R. Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. *Eur J Pharmacol* 1993; **231**:313–314.
- Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *Journal of the American Medical Association* 1992; **267**:64–69.
- Lipton RB, Stewart WF. Migraine in the United States: A review of epidemiology and health care use. *Neurology* 1993; **43**:S6–10.
- Russo E. Cannabis for migraine treatment: The once and future prescription? An historical and scientific review. *Pain* 1998; **76**:3–8.
- Volfe Z, Dvilansky A, Nathan I. Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. *Int J Clin Pharmacol Res* 1985; **5**:243–246.
- Spadone C. Neurophysiologie du cannabis [Neurophysiology of cannabis]. *Encephale* 1991; **17**:17–22.
- Fan P. Cannabinoid agonists inhibit the activation of 5-HT₃ receptors in rat nodose ganglion. *Journal of Neurophysiology* 1995; **73**:907–910.
- Boger DL, Patterson JE, Jin Q. Structural requirements for 5-HT_{2A} and 5-HT_{1A} serotonin receptor potentiation by the biologically active lipid oleamide. *Proc Natl Acad Sci U S A* 1998; **95**:4102–4107.
- Hall B, Burnett A, Christians A, Halley C, Parker LA, Russo E, et al. (2004). Pharmacology of cannabidiol at serotonin receptors. Western Pharmacology Society, Honolulu, HI.
- Russo EB, Macarah CM, Todd CL, Medora R, Parker K. (2000). Pharmacology of the essential oil of hemp at 5HT_{1A} and 5HT_{2a} receptors. 41st Annual Meeting of the American Society of Pharmacognosy, Seattle, WA.
- Kimura T, Ohta T, Watanabe K, Yoshimura H, Yamamoto I. Anandamide, an endogenous cannabinoid receptor ligand, also interacts with 5-hydroxytryptamine (5-HT) receptor. *Biol Pharm Bull* 1998; **21**:224–226.
- Peroutka SJ. The pharmacology of current anti-migraine drugs. *Headache* 1990; **30**:5–11; discussion 24–18.
- Peroutka SJ. Dopamine and migraine. *Neurology* 1997; **49**:650–656.
- Ferri S, Cavicchini E, Romualdi P, Speroni E, Murari G. Possible mediation of catecholaminergic pathways in the antinociceptive effect of an extract of *Cannabis sativa* L. *Psychopharmacology* 1986; **89**:244–247.
- Stefano GB, Salzet B, Rialas CM, Pope M, Kustka A, Neenan K, et al. Morphine- and anandamide-stimulated nitric oxide production inhibits presynaptic dopamine release. *Brain Res* 1997; **763**:63–68.
- Muller-Vahl KR, Schneider U, Prevedel H, Theloe K, Kolbe H, Daldrup T, et al. Delta9-Tetrahydrocannabinol (THC) is Effective in the Treatment of Tics in Tourette Syndrome: a 6-Week Randomized Trial. *J Clin Psychiatry* 2003; **64**:459–465.

- 25 Müller-Vahl KR, Schneider U, Kolbe H, Emrich HM. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. *Am J Psychiatry* 1999; **156**:495.
- 26 Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D. Elevated endogenous cannabinoids in schizophrenia. *Neuroreport* 1999; **10**: 1665-1669.
- 27 Burstein S. Eicosanoids as mediators of cannabinoid action. In: Murphy L, Bartke A, editors. *Marijuana/Cannabinoids: Neurobiology and neurophysiology of drug abuse*. Boca Raton: CRC Press; 1992. p. 73-91.
- 28 Evans AT, Formukong EA, Evans FJ. Actions of cannabis constituents on enzymes of arachidonate metabolism: anti-inflammatory potential. *Biochem Pharmacol* 1987; **36**:2035-2037.
- 29 Formukong EA, Evans AT, Evans FJ. Analgesic and antiinflammatory activity of constituents of *Cannabis sativa* L. *Inflammation* 1988; **12**:361-371.
- 30 Formukong EA, Evans AT, Evans FJ. The inhibitory effects of cannabinoids, the active constituents of *Cannabis sativa* L. on human and rabbit platelet aggregation. *J Pharm Pharmacol* 1989; **41**: 705-709.
- 31 McPartland J. Cannabis and eicosanoids: A review of molecular pharmacology. *Journal of Cannabis Therapeutics* 2001; **1**:71-83.
- 32 Burstein S, Levin E, Varanelli C. Prostaglandins and cannabis. II. Inhibition of biosynthesis by the naturally occurring cannabinoids. *Biochem Pharmacol* 1973; **22**:2905-2910.
- 33 Schaefer CF, Brackett DJ, Gunn CG, Dubowski KM. Decreased platelet aggregation following marijuana smoking in man. *J Okla State Med Assoc* 1979; **72**:435-436.
- 34 Evans FJ. Cannabinoids: The separation of central from peripheral effects on a structural basis. *Planta Med* 1991; **57**:S60-67.
- 35 Hampson AJ, Hill WA, Zan-Phillips M, Makriyannis A, Leung E, Eglen RM, et al. Anandamide hydroxylation by brain lipoxygenase: metabolite structures and potencies at the cannabinoid receptor. *Biochim Biophys Acta* 1995; **1259**:173-179.
- 36 Fimiani C, Liberty T, Aquirre AJ, Amin I, Ali N, Stefano GB. Opiate, cannabinoid, and eicosanoid signaling converges on common intracellular pathways nitric oxide coupling. *Prostaglandins Other Lipid Mediat* 1999; **57**:23-34.
- 37 Fettes I, Gawel M, Kuzniak S, Edmeads J. Endorphin levels in headache syndromes. *Headache* 1985; **25**:37-39.
- 38 Wiegant VM, Sweep CG, Nir I. Effect of acute administration of delta 1-tetrahydrocannabinol on beta- endorphin levels in plasma and brain tissue of the rat. *Experientia* 1987; **43**:413-415.
- 39 Mailleux P, Vanderhaeghen JJ. Delta-9-tetrahydrocannabinol regulates substance P and enkephalin mRNAs levels in the caudate-putamen. *Eur J Pharmacol* 1994; **267**:R1-3.
- 40 Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. *Nature* 1998; **395**:381-383.
- 41 Goadsby PJ, Gundlach AL. Localization of 3H-dihydroergotamine-binding sites in the cat central nervous system: relevance to migraine. *Ann Neurol* 1991; **29**:91-94.
- 42 Lichtman AH, Martin BR. Spinal and supraspinal components of cannabinoid-induced antinociception. *J Pharmacol Exp Ther* 1991; **258**:517-523.
- 43 Behbehani MM. Functional characteristics of the midbrain periaqueductal gray. *Prog Neurobiol* 1995; **46**:575-605.
- 44 Castro ME, Pascual J, Romon T, del Arco C, del Olmo E, Pazos A. Differential distribution of [3H]sumatriptan binding sites (5-HT1B, 5-HT1D and 5-HT1F receptors) in human brain: focus on brainstem and spinal cord. *Neuropharmacology* 1997; **36**:535-542.
- 45 Manzanares J, Corchero J, Romero J, Fernandez-Ruiz JJ, Ramos JA, Fuentes JA. Chronic administration of cannabinoids regulates proenkephalin mRNA levels in selected regions of the rat brain. *Brain Res Mol Brain Res* 1998; **55**:126-132.
- 46 Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC. Pain modulation by the release of the endogenous cannabinoid anandamide. *Proceedings of the National Academy of Sciences* 1999; **96**: 12198-12203.
- 47 Hamann W, di Vadi PP. Analgesic effect of the cannabinoid analogue nabilon is not mediated by opioid receptors. *Lancet* 1999; **353**: 560.
- 48 Nicolodi M. Painful and non-painful effects of low doses of morphine in migraine sufferers partly depend on excitatory amino acids and gamma-aminobutyric acid. *Int J Clin Pharmacol Res* 1998; **18**: 79-85.
- 49 Storer RJ, Goadsby PJ. Trigeminovascular nociceptive transmission involves N-methyl-D-aspartate and non-N-methyl-D-aspartate glutamate receptors. *Neuroscience* 1999; **90**:1371-1376.
- 50 Shen M, Piser TM, Seybold VS, Thayer SA. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *J Neurosci* 1996; **16**:4322-4334.
- 51 Shen M, Thayer SA. Delta-9-tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture. *Mol Pharmacol* 1999; **55**:8-13.
- 52 Nicolodi M, Sicuteri F. Exploration of NMDA receptors in migraine: Therapeutic and theoretic implications. *Int J Clin Pharmacol Res* 1995; **15**:181-189.
- 53 Nicolodi M, Del Bianco PL, Sicuteri F. Modulation of excitatory amino acids pathway: a possible therapeutic approach to chronic daily headache associated with analgesic drugs abuse. *Int J Clin Pharmacol Res* 1997; **17**:97-100.
- 54 Nicolodi M, Sicuteri F. Negative modulators [sic] of excitatory amino acids in episodic and chronic migraine: preventing and reverting chronic migraine. Special lecture 7th INWIN Congress. *Int J Clin Pharmacol Res* 1998; **18**:93-100.
- 55 Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)-Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci U S A* 1998; **95**:8268-8273.
- 56 Main A, Dowson A, Gross M. Photophobia and phonophobia in migraineurs between attacks. *Headache* 1997; **37**:492-495.
- 57 Mechoulam R, Ben-Shabat S. From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: The ongoing story of cannabis. *Nat Prod Rep* 1999; **16**:131-143.
- 58 McPartland JM, Russo EB. Cannabis and cannabis extracts: Greater than the sum of their parts? *Journal of Cannabis Therapeutics* 2001; **1**:103-132.
- 59 Panikashvili D, Simeonidou C, Ben-Shabat S, Hanus L, Breuer A, Mechoulam R, et al. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. *Nature* 2001; **413**:527-531.
- 60 Mikuriya TH. 1997. Chronic migraine headache: Five cases successfully treated with marinol and/or illiciit cannabis.
- 61 Grinspoon L, Bakalar JB. *Marihuana, the forbidden medicine*. 1993. Yale University Press, New Haven.
- 62 el-Mallakh RS. Marijuana and migraine. *Headache* 1987; **27**:442-443.
- 63 Gieringer D. Medical use of cannabis: Experience in California. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: Pharmacology, toxicology, and therapeutic potential*. Binghamton, NY: Haworth Press; 2001. p. 153-170.
- 64 Gieringer D. Medical cannabis potency testing project. *Bulletin of the Multidisciplinary Association for Psychedelic Studies* 1999; **9**: 20-22.
- 65 Bohr T. Problems with myofascial pain syndrome and fibromyalgia syndrome. *Neurology* 1996; **46**:593-597.
- 66 Bennett RM. Rational management of fibromyalgia. *Rheum Dis Clin North Am* 2002; **28**:xiii-xv.
- 67 Nicolodi M, Volpe AR, Sicuteri F. Fibromyalgia and headache. Failure of serotonergic analgesia and N-methyl-D-aspartate-mediated neuronal plasticity: Their common clues. *Cephalalgia* 1998; **18** (Suppl 21):41-44.
- 68 Richardson JD, Aanonsen L, Hargreaves KM. SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice. *Eur J Pharmacol* 1997; **319**:R3-4.
- 69 Richardson JD, Aanonsen L, Hargreaves KM. Hypoactivity of the spinal cannabinoid system results in NMDA-dependent hyperalgesia. *J Neurosci* 1998; **18**:451-457.
- 70 Richardson JD, Aanonsen L, Hargreaves KM. Antihyperalgesic effects of spinal cannabinoids. *Eur J Pharmacol* 1998; **345**:145-153.
- 71 Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain* 1998; **75**:111-119.
- 72 Li J, Daughters RS, Bullis C, Bengiamin R, Stucky MW, Brennan J, et al. The cannabinoid receptor agonist WIN 55,212-2 mesylate blocks the development of hyperalgesia produced by capsaicin in rats. *Pain* 1999; **81**:25-33.
- 73 Ko MC, Woods JH. Local administration of delta9-tetrahydrocannabinol attenuates capsaicin-induced thermal nociception in rhesus monkeys: a peripheral cannabinoid action. *Psychopharmacology (Berl)* 1999; **143**:322-326.
- 74 Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain* 2001; **91**:165-175.
- 75 Strangman NM, Walker JM. Cannabinoid WIN 55,212-2 inhibits the activity-dependent facilitation of spinal nociceptive responses. *J*

- Neurophysiol 1999; **82**:472–477.
- 76 Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol* 1995; **50**:83–90.
 - 77 Holzer P. Gastrointestinal afferents as targets of novel drugs for the treatment of functional bowel disorders and visceral pain. *Eur J Pharmacol* 2001; **429**:177–193.
 - 78 Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* 2001; **134**:845–852.
 - 79 Pertwee RG. Cannabinoids and the gastrointestinal tract. *Gut* 2001; **48**:859–867.
 - 80 Coutts AA, Irving AJ, Mackie K, Pertwee RG, Anavi-Goffer S. Localisation of cannabinoid CB(1) receptor immunoreactivity in the guinea pig and rat myenteric plexus. *J Comp Neurol* 2002; **448**:410–422.
 - 81 Izzo AA, Fezza F, Capasso R, Bisogno T, Pinto L, Iuvone T, et al. Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation. *Br J Pharmacol* 2001; **134**:563–570.
 - 82 Anderson PF, Jackson DM, Chesher GB. Interaction of delta-9-tetrahydrocannabinol and cannabidiol on intestinal motility in mice. *J Pharm Pharmacol* 1974; **26**:136–137.
 - 83 Di Carlo G, Izzo AA. Cannabinoids for gastrointestinal diseases: potential therapeutic applications. *Expert Opin Investig Drugs* 2003; **12**:39–49.
 - 84 Russo E. Cannabinoids in pain management. Study was bound to conclude that cannabinoids had limited efficacy. *Brit Med J* 2001; **323**:1249–1250; discussion 1250–1241.
 - 85 Talley NJ. Evaluation of drug treatment in irritable bowel syndrome. *Br J Clin Pharmacol* 2003; **56**:362–369.
 - 86 Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. *Ann Neurol* 2000; **47**:614–624.
 - 87 Weissman-Fogel I, Sprecher E, Granovsky Y, Yarnitsky D. Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons. *Pain* 2003; **104**:693–700.
 - 88 Nicolodi M, Sicuteri R, Coppola G, Greco E, Pietrini U, Sicuteri F. Visceral pain threshold is deeply lowered far from the head in migraine. *Headache* 1994; **34**:12–19.
 - 89 Nicolodi M, Sicuteri F. Fibromyalgia and migraine, two faces of the same mechanism. In: Filippini GA, editors. Recent advances in tryptophan research. New York: Plenum Press; 1996. p. 373–379.
 - 90 Peres MF, Young WB, Kaup AO, Zukerman E, Silberstein SD. Fibromyalgia is common in patients with transformed migraine. *Neurology* 2001; **57**:1326–1328.
 - 91 Hudson JI, Goldenberg DL, Pope HG, Jr., Keck PE, Jr., Schlesinger L. Comorbidity of fibromyalgia with medical and psychiatric disorders. *Am J Med* 1992; **92**:363–367.
 - 92 Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakra M, et al. Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications. *Am J Gastroenterol* 1999; **94**:3541–3546.
 - 93 Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 1998; **76**:189–199.
 - 94 Jaggar SI, Sellaturay S, Rice AS. The endogenous cannabinoid anandamide, but not the CB2 ligand palmitoylethanolamide, prevents the viscerovisceral hyper-reflexia associated with inflammation of the rat urinary bladder. *Neurosci Lett* 1998; **253**:123–126.
 - 95 Brady CM, DasGupta R, Wiseman OJ, Berkley KJ, Fowler CJ. (2001). Congress of the International Association for Cannabis as Medicine, Berlin, Germany.
 - 96 Verne GN, Robinson ME, Vase L, Price DD. Reversal of visceral and cutaneous hyperalgesia by local rectal anesthesia in irritable bowel syndrome (IBS) patients. *Pain* 2003; **105**:223–230.
 - 97 Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 2000; **404**:84–87.
 - 98 Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; **362**:1517–1526.
 - 99 Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clinical Rehabilitation* 2003; **17**:18–26.
 - 100 Ferrari F, Ottani A, Giuliani D. Inhibitory effects of the cannabinoid agonist HU 210 on rat sexual behaviour. *Physiol Behav* 2000; **69**:547–554.
 - 101 Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmonds S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 “N of 1” studies. *Anaesthesia* 2004; **59**:440–452.
 - 102 Jarvinen T, Pate D, Laine K. Cannabinoids in the treatment of glaucoma. *Pharmacol Ther* 2002; **95**:203.
 - 103 Russo E. Cannabis treatments in obstetrics and gynecology: A historical review. *Journal of Cannabis Therapeutics* 2002; **2**:5–35.
 - 104 Pertwee RG, Ross RA. Cannabinoid receptors and their ligands. *Prostaglandins Leukot Essent Fatty Acids* 2002; **66**:101–121.
 - 105 Williams SJ, Hartley JP, Graham JD. Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax* 1976; **31**:720–723.
 - 106 Fride E. Cannabinoids and cystic fibrosis: A novel approach. *Journal of Cannabis Therapeutics* 2002; **2**:59–71.
 - 107 Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J Psychoactive Drugs* 1998; **30**:171–177.
 - 108 Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, et al. The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 2002; **418**:530–534.
 - 109 Wallace MJ, Martin BR, DeLorenzo RJ. Evidence for a physiological role of endocannabinoids in the modulation of seizure threshold and severity. *Eur J Pharmacol* 2002; **452**:295–301.
 - 110 Wallace MJ, Blair RE, Falenski KW, Martin BR, DeLorenzo RJ. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 2003; **307**:129–137.
 - 111 Delgado P, Moreno F. Antidepressants and the brain. *Int Clin Psychopharmacol* 1999; **14 Suppl 1**:S9–16.
 - 112 Baker D, Pryce G, Giovannoni G, Thompson AJ. The therapeutic potential of cannabis. *Lancet Neurology* 2003; **2**:291–298.
 - 113 Mechoulam R, Panikashvili D, Shohami E. Cannabinoids and brain injury: therapeutic implications. *Trends Mol Med* 2002; **8**:58–61.
 - 114 Guzman M. Cannabinoids: potential anticancer agents. *Nat Rev Cancer* 2003; **3**:745–755.
 - 115 Maccarrone M, Finazzi-Agro A. The endocannabinoid system, anandamide and the regulation of mammalian cell apoptosis. *Cell Death Differ* 2003; **10**:946–955.
 - 116 Hillard CJ, Jarrarian A. Cellular accumulation of anandamide: consensus and controversy. *Br J Pharmacol* 2003; **140**:802–808.
 - 117 Porter AC, Sauer JM, Knierman MD, Becker GW, Berna MJ, Bao J, et al. Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor. *J Pharmacol Exp Ther* 2002; **301**:1020–1024.
 - 118 Russo EB. Cannabis-From pariah to prescription. *Journal of Cannabis Therapeutics* 2003; **3**(3):1–29.
 - 119 Whittle BA, Guy GW, Robson P. Prospects for new cannabis-based prescription medicines. *Journal of Cannabis Therapeutics* 2001; **1**:183–205.
 - 120 Whittle BA, Guy GW, Robson P. Cannabis and cannabinoids as medicines. 2003. Pharmaceutical Press, London.