

Ethan B. Russo and Andrea G. Hohmann

## Key Points

- Cannabinoids are pharmacological agents of endogenous (endocannabinoids), botanical (phytocannabinoids), or synthetic origin.
- Cannabinoids alleviate pain through a variety of receptor and non-receptor mechanisms including direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, and interactions with endogenous and administered opioids.
- Cannabinoid agents are currently available in various countries for pain treatment, and even cannabinoids of botanical origin may be approvable by FDA, although this is distinctly unlikely for smoked cannabis.
- An impressive body of literature supports cannabinoid analgesia, and recently, this has been supplemented by an increasing number of phase I–III clinical trials.

and their role in inflammation. The opium poppy (*Papaver somniferum*) provided the prototypic narcotic analgesic morphine, the first alkaloid discovered, and stimulated the much later discovery of the endorphin and enkephalin systems. Similarly, the pharmacological properties of cannabis (*Cannabis sativa*) prompted the isolation of  $\Delta^9$ -tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, in 1964 [2]. It is this breakthrough that subsequently prompted the more recent discovery of the body's own cannabis-like system, the endocannabinoid system (ECS), which modulates pain under physiological conditions. Pro-nociceptive mechanisms of the endovanilloid system were similarly revealed by phytochemistry of capsaicin, the pungent ingredient in hot chile peppers (*Capsicum annuum* etc.), which activates transient receptor potential vanilloid receptor-1 (TRPV1). Additional plant products such as the mints and mustards activate other TRP channels to produce their physiological effects.

## Introduction

### Plants and Pain

It is a curious fact that we owe a great deal of our insight into pharmacological treatment of pain to the plant world [1]. Willow bark from *Salix* spp. led to development of aspirin and eventual elucidation of the analgesic effects of prostaglandins

## The Endocannabinoid System

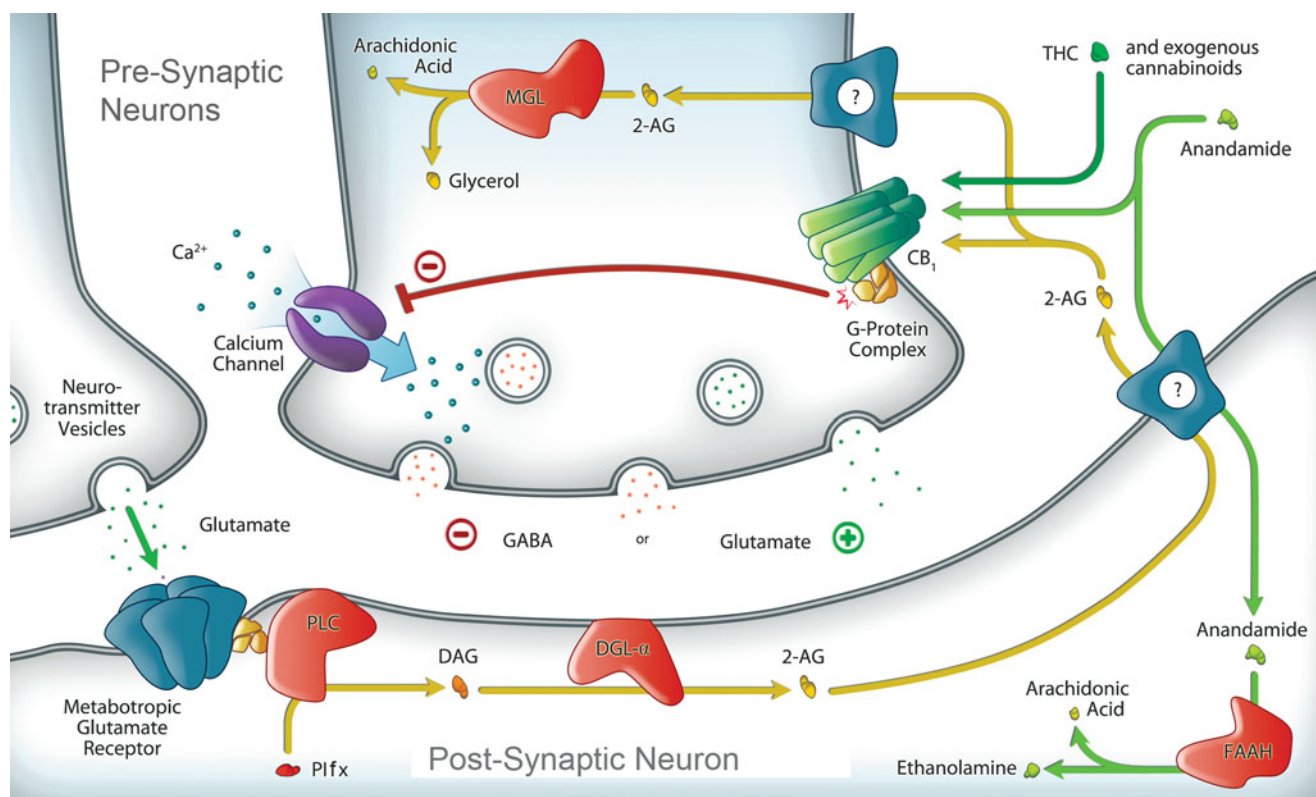
There are three recognized types of cannabinoids: (1) the phytocannabinoids [3] derived from the cannabis plant, (2) synthetic cannabinoids (e.g., ajulemic acid, nabilone, CP55940, WIN55, 212-2) based upon the chemical structure of THC or other ligands which bind cannabinoid receptors, and (3) the endogenous cannabinoids or endocannabinoids. Endocannabinoids are natural chemicals such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) found in animals whose basic functions are “relax, eat, sleep, forget, and protect” [4]. The endocannabinoid system encompasses the endocannabinoids themselves, their biosynthetic and catabolic enzymes, and their corresponding receptors [5]. AEA is hydrolyzed by the enzyme fatty-acid amide hydrolase (FAAH) into breakdown products arachidonic acid and ethanolamine [6]. By contrast, 2-AG is hydrolyzed primarily by the enzyme monoacylglycerol lipase (MGL) into breakdown products arachidonic acid and glycerol [7] and to a lesser extent by the enzymes ABHD6 and ABHD12. FAAH, a

---

E.B. Russo, M.D. (✉)  
GW Pharmaceuticals,  
20402 81st Avenue SW, Vashon, WA 98070, USA

Pharmaceutical Sciences, University of Montana,  
Missoula, MT, USA  
e-mail: ethanrusso@comcast.net

A.G. Hohmann, Ph.D.  
Department of Psychological and Brain Sciences, Indiana University,  
101 East 10th Street, Bloomington, IN 47405, USA  
e-mail: hohmanna@indiana.edu



**Fig. 18.1** Putative mechanism of endocannabinoid-mediated retrograde signaling in the nervous system. Activation of metabotropic glutamate receptors (*mGluR*) by glutamate triggers the activation of the phospholipase C (*PLC*)-diacylglycerol lipase (*DGL*) pathway to generate the endocannabinoid 2-arachidonoylglycerol (2-AG). First, the 2-AG precursor diacylglycerol (*DAG*) is formed from *PLC*-mediated hydrolysis of membrane phospholipid precursors (*PIP<sub>x</sub>*). *DAG* is then hydrolyzed by the enzyme *DGL-α* to generate 2-AG. 2-AG is released from the postsynaptic neuron and acts as a retrograde signaling molecule. Endocannabinoids activate presynaptic *CB<sub>1</sub>* receptors which reside on terminals of glutamatergic and GABAergic neurons. Activation of *CB<sub>1</sub>* by 2-AG, anandamide, or exogenous cannabinoids (e.g., tetrahydrocannabinol, *THC*) inhibits calcium influx in the presynaptic terminal, thereby inhibiting release of the primary neurotransmitter

(i.e., glutamate or GABA) from the synaptic vesicle. Endocannabinoids are then rapidly deactivated by transport into cells (via a putative endocannabinoid transporter) followed by intracellular hydrolysis. 2-AG is metabolized by the enzyme monoacylglycerol lipase (*MGL*), whereas anandamide is metabolized by a distinct enzyme, fatty-acid amide hydrolase (*FAAH*). Note that *MGL* co-localizes with *CB<sub>1</sub>* in the presynaptic terminal, whereas *FAAH* is localized to postsynaptic sites. The existence of an endocannabinoid transporter remains controversial. Pharmacological inhibitors of either endocannabinoid deactivation (e.g., *FAAH* and *MGL* inhibitors) or transport (i.e., uptake inhibitors) have been developed to exploit the therapeutic potential of the endocannabinoid signaling system in the treatment of pain (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

postsynaptic enzyme, may control anandamide levels near sites of synthesis, whereas *MGL*, a presynaptic enzyme [8], may terminate 2-AG signaling following *CB<sub>1</sub>* receptor activation. These enzymes also represent therapeutic targets because inhibition of endocannabinoid deactivation will increase levels of endocannabinoids at sites with ongoing synthesis and release [9]. The pathways controlling formation of AEA remain poorly understood. However, 2-AG is believed to be formed from membrane phospholipid precursors through the sequential activation of two distinct enzymes, phospholipase C and diacylglycerol lipase- $\alpha$ . First, *PLC* catalyzes formation of the 2-AG precursor diacylglycerol (*DAG*) from membrane phosphoinositides. Then, *DAG* is hydrolyzed by the enzyme diacylglycerol lipase- $\alpha$  (*DGL-α*) to generate 2-AG [199].

There are currently two well-defined cannabinoid receptors, although additional candidate cannabinoid receptors have also been postulated. *CB<sub>1</sub>*, a seven transmembrane spanning G-protein-coupled receptor inhibiting cyclic AMP release, was identified in 1988 [10]. *CB<sub>1</sub>* is the primary neuromodulatory receptor accounting for psychopharmacological effects of *THC* and most of its analgesic effects [11]. Endocannabinoids are produced on demand in postsynaptic cells and engage presynaptic *CB<sub>1</sub>* receptors through a retrograde mechanism [12]. Activation of presynaptic *CB<sub>1</sub>* receptors then acts as a synaptic circuit breaker to inhibit neurotransmitter release (either excitatory or inhibitory) from the presynaptic neuron (*vide infra*) (Fig. 18.1). *CB<sub>2</sub>* was identified in 1992, and while thought of primarily as a peripheral immunomodulatory receptor, it also has important

effects on pain. The role of CB<sub>2</sub> in modulating persistent inflammatory and neuropathic pain [13] has been recently reviewed [14, 15]. Activation of CB<sub>2</sub> suppresses neuropathic pain mechanisms through nonneuronal (i.e., microglia and astrocytes) and neuronal mechanisms that may involve interferon-gamma [16]. THC, the prototypical classical cannabinoid, is a weak partial agonist at both CB<sub>1</sub> and CB<sub>2</sub> receptors. Transgenic mice lacking cannabinoid receptors (CB<sub>1</sub>, CB<sub>2</sub>, GPR55), enzymes controlling endocannabinoid breakdown (FAAH, MGL, ABHD6), and endocannabinoid synthesis (DGL- $\alpha$ , DGL- $\beta$ ) have been generated [17]. These knock-outs have helped elucidate the role of the endocannabinoid system in controlling nociceptive processing and facilitated development of inhibitors of endocannabinoid breakdown (FAAH, MGL) as novel classes of analgesics.

## A Brief Scientific History of Cannabis and Pain

### Centuries of Citations

Cannabis has been utilized in one form or another for treatment of pain for longer than written history [18–21]. Although this documentation has been a major preoccupation of the lead author [22–25], and such information can provide provocative direction to inform modern research on treatment of pain and other conditions, it does not represent evidence of form, content, or degree that is commonly acceptable to governmental regulatory bodies with respect to pharmaceutical development.

### Anecdotes Versus Modern Proof of Concept

While thousands of compelling stories of efficacy of cannabis in pain treatment certainly underline the importance of properly harnessing cannabinoid mechanisms therapeutically [26, 27], prescription analgesics in the United States necessitate Food and Drug Administration (FDA) approval. This requires a rigorous development program proving consistency, quality, efficacy, and safety as defined by basic scientific studies and randomized controlled trials (RCT) [28] and generally adhering to recent IMMPACT recommendations [29], provoking our next question.

### Can a Botanical Agent Become a Prescription Medicine?

Most modern physicians fail to recognize that pharmacognosy (study of medicinal plants) has led directly or indirectly to an estimated 25 % of modern pharmaceuticals [30]. While the plethora of available herbal agents yield an indecipherable

cacophony to most clinicians and consumers alike, it is certainly possible to standardize botanical agents and facilitate their recommendation based on sound science [31]. Botanical medicines can even fulfill the rigorous dictates of the FDA and attain prescription drug status via a clear roadmap in the form of a blueprint document [32], henceforth termed the *Botanical Guidance*: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf>. To be successful and clinically valuable, botanicals, including cannabis-based medicines, must demonstrate the same quality, clinical analgesic benefit, and appropriately safe adverse event profile as available new chemical entities (NCE) [28].

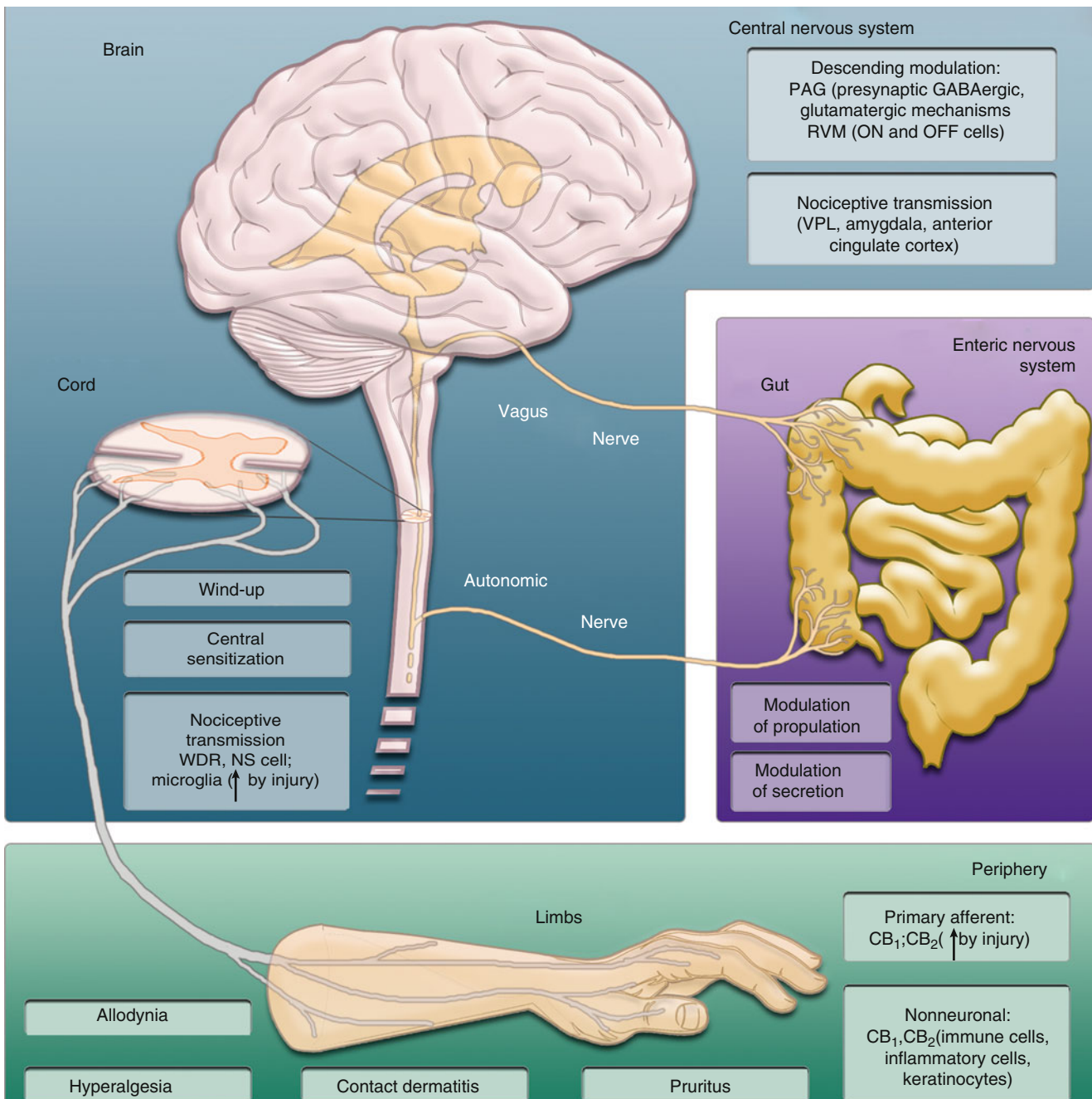
## The Biochemical and Neurophysiological Basis of Pain Control by Cannabinoids

### Neuropathic Pain

Thorough reviews of therapeutic effects of cannabinoids in preclinical and clinical domains have recently been published [33, 34]. In essence, the endocannabinoid system (ECS) is active throughout the CNS and PNS in modulating pain at spinal, supraspinal, and peripheral levels. Endocannabinoids are produced on demand in the CNS to dampen sensitivity to pain [35]. The endocannabinoid system is operative in such key integrative pain centers as the periaqueductal grey matter [36, 37], the ventroposterolateral nucleus of the thalamus [38], and the spinal cord [39, 40]. Endocannabinoids are endogenous mediators of stress-induced analgesia and fear-conditioned analgesia and suppress pain-related phenomena such as windup [41] and allodynia [42]. In the periphery and PNS [13], the ECS has key effects in suppressing both hyperalgesia and allodynia via CB<sub>1</sub> [43] and CB<sub>2</sub> mechanisms (Fig. 18.2). Indeed, pathological pain states have been postulated to arise, at least in part, from a dysregulation of the endocannabinoid system.

### Antinociceptive and Anti-inflammatory Pain Mechanisms

Beyond the mechanisms previously mentioned, the ECS plays a critical role in peripheral pain, inflammation, and hyperalgesia [43] through both CB<sub>1</sub> and CB<sub>2</sub> mechanisms. CB<sub>1</sub> and CB<sub>2</sub> mechanisms are also implicated in regulation of contact dermatitis and pruritus [44]. A role for spinal CB<sub>2</sub> mechanisms, mediated by microglia and/or astrocytes, is also revealed under conditions of inflammation [45]. Both THC and cannabidiol (CBD), a non-euphoriant phytocannabinoid common in certain cannabis strains, are potent anti-inflammatory antioxidants with activity exceeding that of



**Fig. 18.2** Cannabinoids suppress pain and other pathophysiological (e.g., contact dermatitis, pruritis) and physiological (e.g., gastrointestinal transit and secretion) processes through multiple mechanisms involving CB<sub>1</sub> and CB<sub>2</sub> receptors. Peripheral, spinal, and supraspinal sites of cannabinoid actions are shown. In the periphery, cannabinoids act through both neuronal and nonneuronal mechanisms to control inflammation, allodynia, and hyperalgesia. CB<sub>1</sub> and CB<sub>2</sub> have been localized to both primary afferents and nonneuronal cells (e.g., keratinocytes, microglia), and expression can be regulated by injury. In the spinal cord, cannabinoids suppress nociceptive transmission, windup, and central sensitization by modulating activity in the ascending pain

pathway of the spinothalamic tract, including responses of wide dynamic range (*WDR*) and nociceptive specific (*NS*) cells. Similar processes are observed at rostral levels of the neuraxis (e.g., ventroposterolateral nucleus of the thalamus, amygdala, anterior cingulate cortex). Cannabinoids also actively modulate pain through descending mechanisms. In the periaqueductal gray, cannabinoids act through presynaptic glutamatergic and GABAergic mechanisms to control nociception. In the rostral ventromedial medulla, cannabinoids suppress activity in ON cells and inhibit the firing pause of OFF cells, in response to noxious stimulation to produce antinociception (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

vitamins C and E via non-cannabinoid mechanisms [46]. THC inhibits prostaglandin E-2 synthesis [47] and stimulates lipoxygenase [48]. Neither THC nor CBD affects COX-1 or COX-2 at relevant pharmacological dosages [49].

While THC is inactive at vanilloid receptors, CBD, like AEA, is a TRPV<sub>1</sub> agonist. Like capsaicin, CBD is capable of inhibiting fatty-acid amide hydrolase (FAAH), the enzyme which hydrolyzes AEA and other fatty-acid amides that do not bind to cannabinoid receptors. CBD additionally inhibits AEA reuptake [50] though not potently. Thus, CBD acts as an endocannabinoid modulator [51], a mechanism that various pharmaceutical firms hope to emulate with new chemical entities (NCEs). CBD inhibits hepatic metabolism of THC to 11-hydroxy-THC, which is possibly more psychoactive, and prolongs its half-life, reducing its psychoactivity and attenuating attendant anxiety and tachycardia [51]; antagonizes psychotic symptoms [52]; and attenuates appetitive effects of THC [53] as well as its effects on short-term memory [54]. CBD also inhibits tumor necrosis factor-alpha (TNF- $\alpha$ ) in a rodent model of rheumatoid arthritis [55]. Recently, CBD has been demonstrated to enhance adenosine receptor A2A signaling via inhibition of the adenosine transporter [56].

Recently, GPR18 has been proposed as a putative CBD receptor whose function relates to cellular migration [57]. Antagonism of GPR18 (by agents such as CBD) may be efficacious in treating pain of endometriosis, among other conditions, especially considering that such pain may be endocannabinoid-mediated [58]. Cannabinoids are also very active in various gastrointestinal and visceral sites mediating pain responses [59, 60].

### **Cannabinoid Interactions with Other Neurotransmitters Pertinent to Pain**

As alluded to above, the ECS modulates neurotransmitter release via retrograde inhibition. This is particularly important in NMDA-glutamatergic mechanisms that become hyperresponsive in chronic pain states. Cannabinoids specifically inhibit glutamate release in the hippocampus [61]. THC reduces NMDA responses by 30–40 % [46]. Secondary and tertiary hyperalgesia mediated by NMDA [62] and by calcitonin gene-related peptide [40] may well be targets of cannabinoid therapy in disorders such as migraine, fibromyalgia, and idiopathic bowel syndrome wherein these mechanisms seem to operate pathophysiologically [63], prompting the hypothesis of a “clinical endocannabinoid deficiency.” Endocannabinoid modulators may therefore restore homeostasis, leading to normalization of function in these pathophysiological conditions. THC also has numerous effects on serotonergic systems germane to migraine [64], increasing its production in the cerebrum while decreasing reuptake [65]. In fact, the ECS seems to modulate the

trigeminovascular system of migraine pathogenesis at vascular and neurochemical levels [66–68].

### **Cannabinoid-Opioid Interactions**

Although endocannabinoids do not bind to opioid receptors, the ECS may nonetheless work in parallel with the endogenous opioid system with numerous areas of overlap and interaction. Pertinent mechanisms include stimulation of beta-endorphin by THC [69] as well as its ability to demonstrate experimental opiate sparing [70], prevent opioid tolerance and withdrawal [71], and rekindle opioid analgesia after loss of effect [72]. Adjunctive treatments that combine opioids with cannabinoids may enhance the analgesic effects of either agent. Such strategies may permit lower doses of analgesics to be employed for therapeutic benefit in a manner that minimizes incidence or severity of adverse side effects.

---

### **Clinical Trials, Utility, and Pitfalls of Cannabinoids in Pain**

#### **Evidence for Synthetic Cannabinoids**

Oral dronabinol (THC) has been available as the synthetic Marinol<sup>®</sup> since 1985 and is indicated for nausea associated with chemotherapy and appetite stimulation in HIV/AIDS. Issues with its cost, titration difficulties, delayed onset, and propensity to induce intoxicating and dysphoric effects have limited clinical application [73]. It was employed in two open-label studies of chronic neuropathic pain in case studies in 7 [74] and 8 patients [75], but no significant benefit was evident and side effects led to prominent dropout rates (average doses 15–16.6 mg THC). Dronabinol produced benefit in pain in multiple sclerosis [76], but none was evident in post-operative pain (Table 18.1) [77]. Dronabinol was reported to relieve pruritus in three case-report subjects with cholestatic jaundice [78]. Dronabinol was assessed in 30 chronic non-cancer pain patients on opioids in double-blind crossover single-day sessions vs. placebo with improvement [79], followed by a 4-week open-label trial with continued improvement (Table 18.1). Associated adverse events were prominent. Methodological issues included lack of prescreening for cannabinoids, 4 placebo subjects with positive THC assays, and 58 % of subjects correctly guessing Marinol dose on test day. An open-label comparison in polyneuropathy examined nabixone patients with 6 obtaining 22.6 % mean pain relief after 3 months, and 5 achieving 28.6 % relief after 6 months, comparable to conventional agents [80]. A pilot study of Marinol in seven spinal cord injury patients with neuropathic pain saw two withdraw, and the remainder appreciate no greater efficacy than with diphenhydramine [81].

**Table 18.1** Randomized controlled trials of cannabinoids in pain

Agent	N=	Indication	Duration/type	Outcomes/reference
Ajulemic acid	21	Neuropathic pain	7 day crossover	Visual analogue pain scales improved over placebo ( $p=0.02$ )/Karst et al. [92]
Cannabis, smoked	50	HIV neuropathy	5 days/DB	Decreased daily pain ( $p=0.03$ ) and hyperalgesia ( $p=0.05$ ), 52 % with >30 % pain reduction vs. placebo ( $p=0.04$ )/Abrams et al. [94]
Cannabis, smoked	23	Chronic neuropathic pain	5 days/DB	Decreased pain vs. placebo only at 9.4 % THC level ( $p=0.023$ )/Ware et al. [98]
Cannabis, smoked	38	Neuropathic pain	Single dose/DBC	NSD in pain except at highest cannabis dose ( $p=0.02$ ), with prominent psychoactive effects/Wilsey et al. [95]
Cannabis, smoked	34	HIV neuropathy	5 days /DB	DDS improved over placebo ( $p=0.016$ ), 46 % vs. 18 % improved >30 %, 2 cases toxic psychosis/Ellis et al. [97]
Cannabis, vaporized	21	Chronic pain on opioids	5 days/DB	27 % decrement in pain/Abrams et al. [118]
Cannador	419	Pain due to spasm in MS	15 weeks	Improvement over placebo in subjective pain associated with spasm ( $p=0.003$ )/Zajicek et al. [120]
Cannador	65	Postherpetic neuralgia	4 weeks	No benefit observed/Ernst et al. [122]
Cannador	30	Postoperative pain	Single doses, daily	Decreasing pain intensity with increased dose ( $p=0.01$ )/Holdcroft et al. [123]
Marinol	24	Neuropathic pain in MS	15–21 days/DBC	Median numerical pain ( $p=0.02$ ), median pain relief improved ( $p=0.035$ ) over placebo/Svendsen et al. [76]
Marinol	40	Postoperative pain	Single dose/DB	No benefit observed over placebo/Buggy et al. [77]
Marinol	30	Chronic pain	3 doses, 1 day/DBC	Total pain relief improved with 10 mg ( $p<0.05$ ) and 20 mg ( $p<0.01$ ) with opioids, AE prominent/Narang et al. [79]
Nabilone	41	Postoperative pain	3 doses in 24 h/DB	NSD morphine consumption. Increased pain at rest and on movement with nabilone 1 or 2 mg/Beaulieu [85]
Nabilone	31	Fibromyalgia	2 weeks/DBC	Compared to amitriptyline, nabilone improved sleep, decrease wakefulness, had no effect on pain, and increased AE/Ware et al. [90]
Nabilone	96	Neuropathic pain	14 weeks/DBC vs. dihydrocodeine	Dihydrocodeine more effective with fewer AE/Frank et al. [88]
Nabilone	13	Spasticity pain	9 weeks/DBC	NRS decreased 2 points for nabilone ( $p<0.05$ )/Wissel et al. [87]
Nabilone	40	Fibromyalgia	4 weeks/DBC	VAS decreased in pain, Fibromyalgia Impact Questionnaire, and anxiety over placebo (all, $p<0.02$ )/Skrabek et al. [89]
Sativex	20	Neurogenic pain	Series of 2-week N-of-1 crossover blocks	Improvement with Tetranabinex and Sativex on VAS pain vs. placebo ( $p<0.05$ ), symptom control best with Sativex ( $p<0.0001$ )/Wade et al. [132]
Sativex	24	Chronic intractable pain	12 weeks, series of N-of-1 crossover blocks	VAS pain improved over placebo ( $p<0.001$ ) especially in MS ( $p<0.0042$ )/Notcutt et al. [133]
Sativex	48	Brachial plexus avulsion	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with Tetranabinex ( $p=0.002$ ) and Sativex ( $p=0.005$ ) over placebo/Berman et al. [134]
Sativex	66	Central neuropathic pain in MS	5 weeks	Numerical Rating Scale (NRS) analgesia improved over placebo ( $p=0.009$ )/Rog et al. [135]

(continued)

**Table 18.1** (continued)

Agent	N=	Indication	Duration/type	Outcomes/reference
Sativex	125	Peripheral neuropathic pain	5 weeks	Improvements in NRS pain levels ( $p=0.004$ ), dynamic allodynia ( $p=0.042$ ), and punctuate allodynia ( $p=0.021$ ) vs. placebo/Nurmikko et al. [136]
Sativex	56	Rheumatoid arthritis	Nocturnal dosing for 5 weeks	Improvements over placebo morning pain on movement ( $p=0.044$ ), morning pain at rest ( $p=0.018$ ), DAS-28 ( $p=0.002$ ), and SF-MPQ pain at present ( $p=0.016$ )/Blake et al. [138]
Sativex	117	Pain after spinal injury	10 days	NSD in NRS pain scores, but improved Brief Pain Inventory ( $p=0.032$ ), and Patients' Global Impression of Change ( $p=0.001$ ) (unpublished)
Sativex	177	Intractable cancer pain	2 weeks	Improvements in NRS analgesia vs. placebo ( $p=0.0142$ ), Tetranabinex NSD/Johnson et al. [139]
Sativex	135	Intractable lower urinary tract symptoms in MS	8 weeks	Improved bladder severity symptoms including pain over placebo ( $p=0.001$ ) [200]
Sativex	360	Intractable cancer pain	5 weeks/DB	CRA of lower and middle-dose cohorts improved over placebo ( $p=0.006$ ) [201]

Nabilone, or Cesamet®, is a semisynthetic analogue of THC that is about tenfold more potent, and longer lasting [82]. It is indicated as an antiemetic in chemotherapy in the USA. Prior case reports in neuropathic pain [83] and other pain disorders [84] have been published. Sedation and dysphoria are prominent associated adverse events. An RCT of nabilone in 41 postoperative subjects dosed TID actually resulted in increased pain scores (Table 18.1) [85]. An uncontrolled study of 82 cancer patients on nabilone noted improved pain scores [86], but retention rates were limited. Nabilone improved pain ( $p<0.05$ ) vs. placebo in patients with mixed spasticity syndromes in a small double-blind trial (Table 18.1) [87], but was without benefits in other parameters. In a double-blind crossover comparison of nabilone to dihydrocodeine (schedule II opioid) in chronic neuropathic pain (Table 18.1) [88], both drugs produced marginal benefit, but with dihydrocodeine proving clearly superior in efficacy and modestly superior in side-effect profile. In an RCT in 40 patients of nabilone vs. placebo over 4 weeks, it showed significant decreases in VAS of pain and anxiety (Table 18.1) [89]. A more recent study of nabilone vs. amitriptyline in fibromyalgia yielded benefits on sleep, but not pain, mood, or quality of life (Table 18.1) [90]. An open-label trial of nabilone vs. gabapentin found them comparable in pain and other symptom relief in peripheral neuropathic pain [91].

Ajulemic acid (CT3), another synthetic THC analogue in development, was utilized in a phase II RCT in peripheral neuropathic pain in 21 subjects with apparent improvement (Table 18.1) [92]. Whether or not ajulemic acid is psychoactive is the subject of some controversy [93].

### Evidence for Smoked or Vaporized Cannabis

Few randomized controlled clinical trials (RCTs) of pain with smoked cannabis have been undertaken to date [94–97]. One of these [96] examined cannabis effects on experimental pain in normal volunteers.

Abrams et al. [94] studied inpatient adults with painful HIV neuropathy in 25 subjects in double-blind fashion to receive either smoked cannabis as 3.56 % THC cigarettes or placebo cigarettes three times daily for 5 days (Table 18.1). The smoked cannabis group had a 34 % reduction in daily pain vs. 17 % in the placebo group ( $p=0.03$ ). The cannabis cohort also had a 52 % of subjects report a >30 % reduction in pain scores over the 5 days vs. 24 % in the placebo group ( $p=0.04$ ) (Table 18.1). The authors rated cannabis as “well tolerated” due to an absence of serious adverse events (AE) leading to withdrawal, but all subjects were cannabis experienced. Symptoms of possible intoxication in the cannabis group including anxiety (25 %), sedation (54 %), disorientation (16 %), paranoia (13 %), confusion (17 %), dizziness (15 %), and nausea (11 %) were all statistically significantly more common than in the placebo group. Despite these findings, the authors stated that the values do not represent any serious safety concern in this short-term study. No discussion in the article addressed issues of the relative efficacy of blinding in the trial.

Wilsey et al. [95] examined neuropathic pain in 38 subjects in a double-blind crossover study comparing 7 % THC cannabis, 3.5 % THC cannabis, and placebo cigarettes via a complex cumulative dosing scheme with each dosage given

once, in random order, with at least 3 day intervals separating sessions (Table 18.1). A total of 9 puffs maximum were allowed over several hours per session. Authors stated, "Psychoactive effects were minimal and well-tolerated, but neuropsychological impairment was problematic, particularly with the higher concentration of study medication." Again, only cannabis-experienced subjects were allowed entry. No withdrawals due to AE were reported, but 1 subject was removed due to elevated blood pressure. No significant differences were noted in pain relief in the two cannabis potency groups, but a significant separation of pain reduction from placebo ( $p=0.02$ ) was not evident until a cumulative 9 puffs at 240 min elapsed time. Pain unpleasantness was also reduced in both active treatment groups ( $p<0.01$ ). Subjectively, an "any drug effect" demonstrated a visual analogue scale (VAS) of 60/100 in the high-dose group, but even the low-dose group registered more of a "good drug effect" than placebo ( $p<0.001$ ). "Bad drug effect" was also evident. "Feeling high" and "feeling stoned" were greatest in the high-dose sessions ( $p<0.001$ ), while both high- and low-dose differentiated significantly from placebo ( $p<0.05$ ). Of greater concern, both groups rated impairment as 30/100 on VAS vs. placebo ( $p=0.003$ ). Sedation also demarcated both groups from placebo ( $p<0.01$ ), as did confusion ( $p=0.03$ ), and hunger ( $p<0.001$ ). Anxiety was not considered a prominent feature in this cannabis-experienced population. This study distinguished itself from some others in its inclusion of specific objective neuropsychological measures and demonstrated neurocognitive impairment in attention, learning, and memory, most noteworthy with 7% THC cannabis. No commentary on blinding efficacy was included.

Ellis et al. [97] examined HIV-associated neuropathic pain in a double-blind trial of placebo vs. 1–8% THC cannabis administered four times daily over 5 days with a 2-week washout (Table 18.1). Subjects were started at 4% THC and then titrated upward or downward in four smoking sessions dependent upon their symptom relief and tolerance of the dose. In this study, 96% of subjects were cannabis-experienced, and 28 out of 34 subjects completed the trial. The primary outcome measure (Descriptor Differential Scale, DDS) was improved in the active group over placebo ( $p=0.016$ ), with >30% relief noted in 46% of cannabis subjects vs. 18% of placebo. While most adverse events (AE) were considered mild and self-limited, two subjects had to leave the trial due to toxicity. One cannabis-naïve subject was withdrawn due to "an acute cannabis-induced psychosis" at what proved to be his first actual cannabis exposure. The other subject suffered intractable cough. Pain reduction was greater in the cannabis-treated group ( $p=0.016$ ) among completers, as was the proportion of subjects attaining >30% pain reduction (46% vs. 18%,  $p=0.043$ ). Blinding was assessed in this study; whereas placebo patients were inaccurate at guessing the investigational product, 93% of those

receiving cannabis guessed correctly. On safety issues, the authors stated that the frequency of some nontreatment-limiting side effects was greater for cannabis than placebo. These included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst.

A Canadian study [98] examined single 25-mg inhalations of various cannabis potencies (0–9.4% THC) three times daily for 5 days per cycle in 23 subjects with chronic neuropathic pain (Table 18.1). Patients were said to be cannabis-free for 1 year, but were required to have some experience of the drug. Only the highest potency demarcated from placebo on decrements in average daily pain score (5.4 vs. 6.1,  $p=0.023$ ). The most frequent AE in the high-dose group were headache, dry eyes, burning sensation, dizziness, numbness, and cough, but with "high" or "euphoria" reported only once in each cannabis potency group.

The current studies of smoked cannabis are noteworthy for their extremely short-term exposure and would be of uncertain relevance in a regulatory environment. The IMMPACT recommendations on chronic neuropathic pain clinical trials that are currently favored by the FDA [29] generally suggest randomized controlled clinical trials of 12-week duration as a prerequisite to demonstrate efficacy and safety. While one might assume that the degree of pain improvement demonstrated in these trials could be maintained over this longer interval, it is only reasonable to assume that cumulative adverse events would also increase to at least some degree. The combined studies represent only a total of 1,106 patient-days of cannabis exposure (Abrams: 125, Wilsey: 76, Ellis: 560, Ware 345) or 3 patient-years of experience. In contrast, over 6,000 patient-years of data have been analyzed for Sativex between clinical trials, prescription, and named-patient supplies, with vastly lower AE rates (data on file, GW Pharmaceuticals) [28, 99]. Certainly, the cognitive effects noted in California-smoked cannabis studies figure among many factors that would call the efficacy of blinding into question for investigations employing such an approach. However, it is also important to emphasize that unwanted side effects are not unique to cannabinoids. In a prospective evaluation of specific chronic polyneuropathy syndromes and their response to pharmacological therapies, the presence of intolerable side effects did not differ in groups receiving gabapentinoids, tricyclic antidepressants, anticonvulsants, cannabinoids (including nabilone, Sativex), and topical agents [80]. Moreover, no serious adverse events were related to any of the medications.

The current studies were performed in a very select subset of patients who almost invariably have had prior experience of cannabis. Their applicability to cannabis-naïve populations is, thus, quite unclear. At best, the observed benefits might possibly accrue to some, but it is eminently likely that candidates for such therapy might refuse it on any number of



grounds: not wishing to smoke, concern with respect to intoxication, etc. Sequelae of smoking in therapeutic outcomes have had little discussion in these brief RCTs [28]. Cannabis smoking poses substantial risk of chronic cough and bronchitic symptoms [100], if not obvious emphysematous degeneration [101] or increase in aerodigestive cancers [102]. Even such smoked cannabis proponents as Lester Grinspoon has acknowledged are the only well-confirmed deleterious physical effect of marijuana is harm to the pulmonary system [103]. However, population-based studies of cannabis trials have failed to show any evidence for increased risk of respiratory symptoms/chronic obstructive pulmonary disease [100] or lung cancer [102] associated with smoking cannabis.

A very detailed analysis and comparison of mainstream and sidestream smoke for cannabis vs. tobacco smoke was performed in Canada [104]. Of note, cannabis smoke contained ammonia ( $\text{NH}_3$ ) at a level of 720  $\mu\text{g}$  per 775 mg cigarette, a figure 20-fold higher than that found in tobacco smoke. It was hypothesized that this finding was likely attributable to nitrate fertilizers. Formaldehyde and acetaldehyde were generally lower in cannabis smoke than in tobacco, but butyraldehyde was higher. Polycyclic aromatic hydrocarbon (PAH) contents were qualitatively similar in the comparisons, but total yield was lower for cannabis mainstream smoke, but higher than tobacco for sidestream smoke. Additionally,  $\text{NO}$ ,  $\text{NO}_x$ , hydrogen cyanide, and aromatic amines concentrations were 3–5 times higher in cannabis smoke than that from tobacco. Possible mutagenic and carcinogenic potential of these various compounds were mentioned. More recently, experimental analysis of cannabis smoke with resultant acetaldehyde production has posited its genotoxic potential to be attributable to reactions that produce DNA adducts [105].

Vaporizers for cannabis have been offered as a harm reduction technique that would theoretically eliminate products of combustion and associated adverse events. The Institute of Medicine (IOM) examined cannabis issues in 1999 [106], and among their conclusions was the following (p. 4): “Recommendation 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.” One proposed technique is vaporization, whereby cannabis is heated to a temperature that volatilizes THC and other components with the goal of reducing or eliminating by-products of combustion, including potentially carcinogenic polycyclic aromatic hydrocarbons, benzene, acetaldehyde, carbon monoxide, toluene, naphthalene, phenol, toluene, hydrogen cyanide, and ammonia. Space limitations permit only a cursory review of available literature [107–115].

A pilot study of the Volcano vaporizer vs. smoking was performed in the USA in 2007 in 18 active cannabis consumers, with only 48 h of presumed abstinence [116]. NIDA 900-mg cannabis cigarettes were employed (1.7, 3.4, and

6.8 % THC) with each divided in two, so that one-half would be smoked or vaporized in a series of double-blind sessions. The Volcano vaporizer produced comparable or slightly higher THC plasma concentrations than smoking. Measured CO in exhaled vapor sessions diminished very slightly, while it increased after smoking ( $p < 0.001$ ). Self-reported visual analogue scales of the associated high were virtually identical in vaporization vs. smoking sessions and increased with higher potency material. A contention was advanced that the absence of CO increase after vaporization can be equated to “little or no exposure to gaseous combustion toxins.” Given that no measures of PAH or other components were undertaken, the assertion is questionable. It was also stated that there were no reported adverse events. Some 12 subjects preferred the Volcano, 2 chose smoking, and 2 had no preference as to technique, making the vaporizer “an acceptable system” and providing “a safer way to deliver THC.”

A recent [202, 117] examined interactions of 3.2 % THC NIDA cannabis vaporized in the Volcano in conjunction with opioid treatment in a 5-day inpatient trial in 21 patients with chronic pain (Table 18.1). All subjects were prior cannabis smokers. Overall, pain scores were reduced from 39.6 to 29.1 on a VAS, a 27 % reduction, by day 5. Pain scores in subjects on morphine fell from 34.8 to 24.1, while in subjects taking oxycodone, scores dropped from 43.8 to 33.6.

The clinical studies performed with vaporizers to date have been very small pilot studies conducted over very limited timeframes (i.e., for a maximum of 5 days). Thus, these studies cannot contribute in any meaningful fashion toward possible FDA approval of vaporized cannabis as a delivery technique, device, or drug under existing policies dictated by the *Botanical Guidance* [32]. It is likewise quite unlikely that the current AE profile of smoked or vaporized cannabis would meet FDA requirements. The fact that all the vaporization trials to date have been undertaken only in cannabis-experienced subjects does not imply that results would generalize to larger patient populations. Moreover, there is certainly no reason to expect AE profiles to be better in cannabis-naïve patients. Additionally, existing standardization of cannabis product and delivery via vaporization seem far off the required marks. Although vaporizers represent an alternate delivery method devoid of the illegality associated with smoked cannabis, the presence of toxic ingredients such as PAH, ammonia, and acetaldehyde in cannabis vapor are unlikely to be acceptable to FDA in any significant amounts. Existing vaporizers still lack portability or convenience [28]. A large Internet survey revealed that only 2.2 % of cannabis users employed vaporization as their primary cannabis intake method [118]. While studies to date have established that lower temperature vaporization in the Volcano, but not necessarily other devices, can reduce the relative amounts of noxious by-products of combustion, it has yet to be demonstrated that they are totally eliminated. Until or unless this goal is achieved, along with

requisite benchmarks of herbal cannabis quality, safety, and efficacy in properly designed randomized clinical trials, vaporization remains an unproven technology for therapeutic cannabinoid administration.

## Evidence for Cannabis-Based Medicines

Cannador is a cannabis extract in oral capsules, with differing THC:CBD ratios [51]. Cannador was utilized in a phase III RCT of spasticity in multiple sclerosis (CAMS) (Table 18.1) [119]. While no improvement was evident in the Ashworth Scale, reduction was seen in spasm-associated pain. Both THC and Cannador improved pain scores in follow-up [120]. Cannador was also employed for postherpetic neuralgia in 65 patients, but without success (Table 18.1) [121, 122]. Slight pain reduction was observed in 30 subjects with postoperative pain (CANPOP) not receiving opiates, but psychoactive side effects were notable (Table 18.1).

Sativex® is a whole-cannabis-based extract delivered as an oromucosal spray that combines a CB<sub>1</sub> and CB<sub>2</sub> partial agonist (THC) with a cannabinoid system modulator (CBD), minor cannabinoids, and terpenoids plus ethanol and propylene glycol excipients and peppermint flavoring [51, 123]. It is approved in Canada for spasticity in MS and under a Notice of Compliance with Conditions for central neuropathic pain in multiple sclerosis and treatment of cancer pain unresponsive to opioids. Sativex is also approved in MS in the UK, Spain, and New Zealand, for spasticity in multiple sclerosis, with further approvals expected soon in some 22 countries around the world. Sativex is highly standardized and is formulated from two *Cannabis sativa* chemovars predominating in THC and CBD, respectively [124]. Each 100 µl pump-action oromucosal spray of Sativex yields 2.7 mg of THC and 2.5 mg of CBD plus additional components. Pharmacokinetic data are available [125–127]. Sativex effects begin within an interval allowing dose titration. A very favorable adverse event profile has been observed in the development program [27, 128]. Most patients stabilize at 8–10 sprays per day after 7–10 days, attaining symptomatic control without undue psychoactive sequelae. Sativex was added to optimized drug regimens in subjects with uncontrolled pain in every RCT (Table 18.1). An Investigational New Drug (IND) application to study Sativex in advanced clinical trials in the USA was approved by the FDA in January 2006 in patients with intractable cancer pain. One phase IIB dose-ranging study has already been completed [201]. Available clinical trials with Sativex have been independently assessed [129, 130].

In a phase II study of 20 patients with neurogenic symptoms [131], significant improvement was seen with both Tetranabinex (high-THC extract without CBD) and Sativex

on pain, with Sativex displaying better symptom control ( $p < 0.0001$ ), with less intoxication (Table 18.1).

In a phase II study of intractable chronic pain in 24 patients [132], Sativex again produced the best results compared to Tetranabinex ( $p < 0.001$ ), especially in MS ( $p < 0.0042$ ) (Table 18.1).

In a phase III study of brachial plexus avulsion ( $N = 48$ ) [133], pain reduction with Tetranabinex and Sativex was about equal (Table 18.1).

In an RCT of 66 MS subjects, mean Numerical Rating Scale (NRS) analgesia favored Sativex over placebo (Table 18.1) [134].

In a phase III trial ( $N = 125$ ) of peripheral neuropathic pain with allodynia [135], Sativex notably alleviated pain levels and dynamic and punctate allodynia (Table 18.1).

In a safety-extension study in 160 subjects with various symptoms of MS [136], 137 patients showed sustained improvements over a year or more in pain and other symptoms [99] without development of any tolerance requiring dose escalation or withdrawal effects in those who voluntarily discontinued treatment suddenly. Analgesia was quickly reestablished upon Sativex resumption.

In a phase II RCT in 56 rheumatoid arthritis sufferers over 5 weeks with Sativex [137], medicine was limited to only 6 evening sprays (16.2 mg THC + 15 mg CBD). By study end, morning pain on movement, morning pain at rest, DAS-28 measure of disease activity, and SF-MPQ pain all favored Sativex (Table 18.1).

In a phase III RCT in intractable cancer pain on opioids ( $N = 177$ ), Sativex, Tetranabinex THC-predominant extract, and placebo were compared [138] demonstrating strongly statistically significant improvements in analgesia for Sativex only (Table 18.1). This suggests that the CBD component in Sativex was necessary for benefit.

In a 2-week study of spinal cord injury pain, NRS of pain was not statistically different from placebo, probably due to the short duration of the trial, but secondary endpoints were positive (Table 18.1). Additionally, an RCT of intractable lower urinary tract symptoms in MS also demonstrated pain reduction (Table 18.1).

The open-label study of various polyneuropathy patients included Sativex patients with 3 obtaining 21.56 % mean pain relief after 3 months (2/3 > 30 %), and 4 achieving 27.6 % relief after 6 months (2/4 > 30 %), comparable to conventional agents [80].

A recently completed RCT of Sativex in intractable cancer pain unresponsive to opioids over 5 weeks was performed in 360 subjects (Table 18.1). Results of a Continuous Response Analysis (CRA) showed improvements over placebo in the low-dose ( $p = 0.08$ ) and middle-dose cohorts ( $p = 0.038$ ) or combined ( $p = 0.006$ ). Pain NRS improved over placebo in the low-dose ( $p = 0.006$ ) and combined cohorts ( $p = 0.019$ ).

Sleep has improved markedly in almost all Sativex RCTs in chronic pain based on symptom reduction, not a hypnotic effect [139].

The adverse event (AE) profile of Sativex has been quite benign with bad taste, oral stinging, dry mouth, dizziness, nausea, or fatigue most common, but not usually prompting discontinuation [128]. Most psychoactive sequelae are early and transient and have been notably lowered by more recent application of a slower, less aggressive titration schedule. While no direct comparative studies have been performed with Sativex and other agents, AE rates were comparable or greater with Marinol than with Sativex employing THC dosages some 2.5 times higher, likely due to the presence of accompanying CBD [28, 51]. Similarly, Sativex displayed a superior AE profile compared to smoked cannabis based on safety-extension studies of Sativex [28, 99], as compared to chronic use of cannabis with standardized government-supplied material in Canada for chronic pain [140] and the Netherlands for various indications [141, 142] over a period of several months or more. All AEs are more frequent with smoked cannabis, except for nausea and dizziness, both early and usually transiently reported with Sativex [27, 28, 128]. A recent meta-analysis suggested that serious AEs associated with cannabinoid-based medications did not differ from placebo and thus could not be attributable to cannabinoid use, further reinforcing the low toxicity associated with activation of cannabinoid systems.

### **Cannabinoid Pitfalls: Are They Surmountable?**

The dangers of COX-1 and COX-2 inhibition by nonsteroidal anti-inflammatory drugs (NSAIDs) of various design (e.g., gastrointestinal ulceration and bleeding vs. coronary and cerebrovascular accidents, respectively) [143, 144] are unlikely to be mimicked by either THC or CBD, which produce no such activity at therapeutic dosages [49].

Natural cannabinoids require polar solvents and may be associated with delayed and sometimes erratic absorption after oral administration. Smoking of cannabis invariably produces rapid spikes in serum THC levels; cannabis smoking attains peak levels of serum THC above 140 ng/ml [145, 146], which, while desirable to the recreational user, has no necessity or advantage for treatment of chronic pain [28]. In contrast, comparable amounts of THC derived from oromucosal Sativex remained below 2 ng/ml with much lower propensity toward psychoactive sequelae [28, 125], with subjective intoxication levels on visual analogue scales that are indistinguishable from placebo, in the single digits out of 100 [100]. It is clear from RCTs that such psychoactivity is not a necessary accompaniment to pain control. In contrast, intoxication has continued to be prominent with oral THC [73].

In comparison to the questionable clinical trial blinding with smoked and vaporized cannabis discussed above, all

indications are that such study blinding has been demonstrably effective with Sativex [147, 148] by utilizing a placebo spray with identical taste and color. Some 50 % of Sativex subjects in RCTs have had prior cannabis exposure, but results of two studies suggest that both groups exhibited comparable results in both treatment efficacy and side effect profile [134, 135].

Controversy continues to swirl around the issue of the potential dangers of cannabis use medicinally, particularly its drug abuse liability (DAL). Cannabis and cannabinoids are currently DEA schedule I substances and are forbidden in the USA (save for Marinol in schedule III and nabilone in schedule II) [73]. This is noteworthy in itself because the very same chemical compound, THC, appears simultaneously in schedule I (as THC), schedule II (as nabilone), and schedule III (as Marinol). DAL is assessed on the basis of five elements: intoxication, reinforcement, tolerance, withdrawal, and dependency plus the drug's overall observed rates of abuse and diversion. Drugs that are smoked or injected are commonly rated as more reinforcing due to more rapid delivery to the brain [149]. Sativex has intermediate onset. It is claimed that CBD in Sativex reduces the psychoactivity of THC [28]. RCT AE profiles do not indicate euphoria or other possible reinforcing psychoactive indicia as common problems with its use [99]. Similarly, acute THC effects such as tachycardia, hypothermia, orthostatic hypotension, dry mouth, ocular injection, and intraocular pressure decreases undergo prominent tachyphylaxis with regular usage [150]. Despite that observation, Sativex has not demonstrated dose tolerance to its therapeutic benefits on prolonged administration, and efficacy has been maintained for up to several years in pain conditions [99].

The existence or severity of a cannabis withdrawal syndrome remains under debate [151, 152]. In contrast to reported withdrawal sequelae in recreational users [153], 24 subjects with MS who volunteered to discontinue Sativex after a year or more suffered no withdrawal symptoms meeting Budney criteria. While symptoms such as pain recurred after some 7–10 days without Sativex, symptom control was rapidly reattained upon resumption [99].

Finally, no known abuse or diversion incidents have been reported with Sativex to date (March 2011). Formal DAL studies of Sativex vs. Marinol and placebo have been completed and demonstrate lower scores on drug liking and similar measures at comparable doses [155].

Cognitive effects of cannabis also remain at issue [155, 156], but less data are available in therapeutic applications. Studies of Sativex in neuropathic pain with allodynia have revealed no changes vs. placebo on Sativex in portions of the Halstead-Reitan Battery [135], or in central neuropathic pain in MS [134], where 80 % of tests showed no significant differences. In a recent RCT of Sativex vs. placebo in MS patients, no cognitive differences of note were observed

[157]. Similarly, chronic Sativex use has not produced observable mood disorders.

Controversies have also arisen regarding the possible association of cannabis abuse and onset of psychosis [156]. However, an etiological relationship is not supported by epidemiological data [158–161], but may well be affected by dose levels and duration, if pertinent. One may speculate that lower serum levels of Sativex combined with antipsychotic properties of CBD [52, 162, 163] might attenuate such concerns. Few cases of related symptoms have been reported in SAFEX studies of Sativex.

Immune function becomes impaired in experimental animals at cannabinoid doses 50–100 times necessary to produce psychoactive effects [164]. In four patients smoking cannabis medicinally for more than 20 years, no changes were evident in leukocyte, CD4, or CD8 cell counts [155]. MS patients on Cannador demonstrated no immune changes of note [165] nor were changes evident in subjects smoking cannabis in a brief trial in HIV patients [166]. Sativex RCTs have demonstrated no hematological or immune dysfunction.

No effects of THC extract, CBD extract, or Sativex were evident on the hepatic cytochrome P450 complex [167] or on human CYP450 [168]. Similarly, while Sativex might be expected to have additive sedative effects with other drugs or alcohol, no significant drug-drug interactions of any type have been observed in the entire development program to date.

No studies have demonstrated significant problems in relation to cannabis affecting driving skills at plasma levels below 5 ng/ml of THC [169]. Four oromucosal sprays of Sativex (exceeding the average single dose employed in therapy) produced serum levels well below this threshold [28]. As with other cannabinoids in therapy, it is recommended that patients not drive nor use dangerous equipment until accustomed to the effects of the drug.

## Future Directions: An Array of Biosynthetic and Phytocannabinoid Analgesics

### Inhibition of Endocannabinoid Transport and Degradation: A Solution?

It is essential that any cannabinoid analgesic strike a compromise between therapeutic and adverse effects that may both be mediated via CB<sub>1</sub> mechanisms [34]. Mechanisms to avoid psychoactive sequelae could include peripherally active synthetic cannabinoids that do not cross the blood-brain barrier or drugs that boost AEA levels by inhibiting fatty-acid amide hydrolase (FAAH) [170] or that of 2-AG by inhibiting monoacylglycerol lipase (MGL). CBD also has this effect [50] and certainly seems to increase the therapeutic index of THC [51].

In preclinical studies, drugs inhibiting endocannabinoid hydrolysis [171, 172] and peripherally acting agonists [173] all

show promise for suppressing neuropathic pain. AZ11713908, a peripherally restricted mixed cannabinoid agonist, reduces mechanical allodynia with efficacy comparable to the brain penetrant mixed cannabinoid agonist WIN55,212-2 [173]. An irreversible inhibitor of the 2-AG hydrolyzing enzyme MGL suppresses nerve injury-induced mechanical allodynia through a CB<sub>1</sub> mechanism, although these anti-allodynic effects undergo tolerance following repeated administration [172]. URB937, a brain impermeant inhibitor of FAAH, has recently been shown to elevate anandamide outside the brain and suppress neuropathic and inflammatory pain behavior without producing tolerance or unwanted CNS side effects [171]. These observations raise the possibility that peripherally restricted endocannabinoid modulators may show therapeutic potential as analgesics with limited side-effect profiles.

## The Phytocannabinoid and Terpenoid Pipeline

Additional phytocannabinoids show promise in treatment of chronic pain [123, 163, 174]. Cannabichromene (CBC), another prominent phytocannabinoid, also displays anti-inflammatory [175] and analgesic properties, though less potently than THC [176]. CBC, like CBD, is a weak inhibitor of AEA reuptake [177]. CBC is additionally a potent TRPA1 agonist [178]. Cannabigerol (CBG), another phytocannabinoid, displays weak binding at both CB<sub>1</sub> and CB<sub>2</sub> [179, 180] but is a more potent GABA reuptake inhibitor than either THC or CBD [181]. CBG is a stronger analgesic, anti-erythema, and lipoxygenase agent than THC [182]. CBG likewise inhibits AEA uptake and is a TRPV1 agonist [177], a TRPA1 agonist, and a TRPM8 antagonist [178]. CBG is also a phospholipase A2 modulator that reduces PGE-2 release in synovial cells [183]. Tetrahydrocannabivarin, a phytocannabinoid present in southern African strains, displays weak CB<sub>1</sub> antagonism [184] and a variety of anticonvulsant activities [185] that might prove useful in chronic neuropathic pain treatment. THCV also reduced inflammation and attendant pain in mouse experiments [187]. Most North American [187] and European [188, 189] cannabis strains have been bred to favor THC over a virtual absence of other phytocannabinoid components, but the latter are currently available in abundance via selective breeding [124, 190].

Aromatic terpenoid components of cannabis also demonstrate pain reducing activity [123, 163]. Myrcene displays an opioid-type analgesic effect blocked by naloxone [191] and reduces inflammation via PGE-2 [192].  $\beta$ -Caryophyllene displays anti-inflammatory activity on par with phenylbutazone via PGE-1 [193], but contrasts by displaying gastric cytoprotective activity [194]. Surprisingly,  $\beta$ -caryophyllene has proven to be a phytocannabinoid in its own right as a selective CB<sub>2</sub> agonist [195].  $\alpha$ -Pinene inhibits PGE-1 [196], and linalool acts as a local anesthetic [197].

## Summary

Basic science and clinical trials support the theoretical and practical basis of cannabinoid agents as analgesics for chronic pain. Their unique pharmacological profiles with multimodality effects and generally favorable efficacy and safety profiles render cannabinoid-based medicines promising agents for adjunctive treatment, particularly for neuropathic pain. It is our expectation that the coming years will mark the advent of numerous approved cannabinoids with varying mechanisms of action and delivery techniques that should offer the clinician useful new tools for treating pain.

## References

- Di Marzo V, Bisogno T, De Petrocellis L. Endocannabinoids and related compounds: walking back and forth between plant natural products and animal physiology. *Chem Biol.* 2007;14(7):741–56.
- Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc.* 1964;86:1646–7.
- Pate D. Chemical ecology of cannabis. *J Int Hemp Assoc.* 1994;2:32–7.
- Di Marzo V, Melck D, Bisogno T, De Petrocellis L. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci.* 1998;21(12):521–8.
- Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev.* 2006;58(3):389–462.
- Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. *Nature.* 1996;384(6604):83–7.
- Dinh TP, Freund TF, Piomelli D. A role for monoglyceride lipase in 2-arachidonoylglycerol inactivation. *Chem Phys Lipids.* 2002;121(1–2):149–58.
- Gulyas AI, Cravatt BF, Bracey MH, et al. Segregation of two endocannabinoid-hydrolyzing enzymes into pre- and postsynaptic compartments in the rat hippocampus, cerebellum and amygdala. *Eur J Neurosci.* 2004;20(2):441–58.
- Mangieri RA, Piomelli D. Enhancement of endocannabinoid signaling and the pharmacotherapy of depression. *Pharmacol Res.* 2007;56(5):360–6.
- Howlett AC, Johnson MR, Melvin LS, Milne GM. Nonclassical cannabinoid analgesics inhibit adenylyl cyclase: development of a cannabinoid receptor model. *Mol Pharmacol.* 1988;33(3):297–302.
- Zimmer A, Zimmer AM, Hohmann AG, Herkenham M, Bonner TI. Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. *Proc Natl Acad Sci USA.* 1999;96(10):5780–5.
- Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. *Nature.* 2001;410(6828):588–92.
- Ibrahim MM, Porreca F, Lai J, et al. CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. *Proc Natl Acad Sci USA.* 2005;102(8):3093–8.
- Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. *Br J Pharmacol.* 2008;153(2):319–34.
- Pacher P, Mechoulam R. Is lipid signaling through cannabinoid 2 receptors part of a protective system? *Prog Lipid Res.* 2011;50:193–211.
- Racz I, Nadal X, Alferink J, et al. Interferon-gamma is a critical modulator of CB(2) cannabinoid receptor signaling during neuropathic pain. *J Neurosci.* 2008;28(46):12136–45.
- Guindon J, Hohmann AG. The endocannabinoid system and pain. *CNS Neurol Disord Drug Targets.* 2009;8(6):403–21.
- Fankhauser M. History of cannabis in Western medicine. In: Grotenhermen F, Russo EB, editors. *Cannabis and cannabinoids: pharmacology, toxicology and therapeutic potential.* Binghamton: Haworth Press; 2002. p. 37–51.
- Russo EB. History of cannabis as medicine. In: Guy GW, Whittle BA, Robson P, editors. *Medicinal uses of cannabis and cannabinoids.* London: Pharmaceutical Press; 2004. p. 1–16.
- Russo EB. History of cannabis and its preparations in saga, science and sobriquet. *Chem Biodivers.* 2007;4(8):2624–48.
- Mechoulam R. The pharmacology of *Cannabis sativa*. In: Mechoulam R, editor. *Cannabinoids as therapeutic agents.* Boca Raton: CRC Press; 1986. p. 1–19.
- Russo E. Cannabis treatments in obstetrics and gynecology: a historical review. *J Cannabis Ther.* 2002;2(3–4):5–35.
- Russo EB. Hemp for headache: an in-depth historical and scientific review of cannabis in migraine treatment. *J Cannabis Ther.* 2001;1(2):21–92.
- Russo EB. The role of cannabis and cannabinoids in pain management. In: Cole BE, Boswell M, editors. *Weiner's pain management: a practical guide for clinicians.* 7th ed. Boca Raton: CRC Press; 2006. p. 823–44.
- Russo EB. Cannabis in India: ancient lore and modern medicine. In: Mechoulam R, editor. *Cannabinoids as therapeutics.* Basel: Birkhäuser Verlag; 2005. p. 1–22.
- ABC News, USA Today, Stanford Medical Center Poll. Broad experience with pain sparks search for relief. 9 May 2005.
- Russo EB. Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag.* 2008;4(1):245–59.
- Russo EB. The solution to the medicinal cannabis problem. In: Schatman ME, editor. *Ethical issues in chronic pain management.* Boca Raton: Taylor & Francis; 2006. p. 165–94.
- Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;113(1–2):9–19.
- Tyler VE. Phytomedicines in Western Europe: potential impact on herbal medicine in the United States. In: Kinghorn AD, Balandrin MF, editors. *Human medicinal agents from plants (ACS symposium, No. 534).* Washington, D.C.: American Chemical Society; 1993. p. 25–37.
- Russo EB. *Handbook of psychotropic herbs: a scientific analysis of herbal remedies for psychiatric conditions.* Binghamton: Haworth Press; 2001.
- Food and Drug Administration. *Guidance for industry: botanical drug products.* In: Services UDoHaH, editor. US Government; 2004. p. 48. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf>.
- Walker JM, Hohmann AG. Cannabinoid mechanisms of pain suppression. *Handb Exp Pharmacol.* 2005;168:509–54.
- Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics.* 2009;6(4):713–37.
- Richardson JD, Aanonsen L, Hargreaves KM. SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice. *Eur J Pharmacol.* 1997;319(2–3):R3–4.
- Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC. Pain modulation by the release of the endogenous cannabinoid anandamide. *Proc Natl Acad Sci.* 1999;96(21):12198–203.
- Walker JM, Hohmann AG, Martin WJ, Strangman NM, Huang SM, Tsou K. The neurobiology of cannabinoid analgesia. *Life Sci.* 1999;65(6–7):665–73.
- Martin WJ, Hohmann AG, Walker JM. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the

- thalamus by a cannabinoid agonist: correlation between electrophysiological and antinociceptive effects. *J Neurosci.* 1996;16:6601–11.
39. Hohmann AG, Martin WJ, Tsou K, Walker JM. Inhibition of noxious stimulus-evoked activity of spinal cord dorsal horn neurons by the cannabinoid WIN 55,212-2. *Life Sci.* 1995;56(23–24):2111–8.
  40. Richardson JD, Aanonsen L, Hargreaves KM. Antihyperalgesic effects of spinal cannabinoids. *Eur J Pharmacol.* 1998;345(2):145–53.
  41. Strangman NM, Walker JM. Cannabinoid WIN 55,212-2 inhibits the activity-dependent facilitation of spinal nociceptive responses. *J Neurophysiol.* 1999;82(1):472–7.
  42. Rahn EJ, Makriyannis A, Hohmann AG. Activation of cannabinoid CB(1) and CB(2) receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. *Br J Pharmacol.* 2007;152:765–77.
  43. Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain.* 1998;75(1):111–9.
  44. Karsak M, Gaffal E, Date R, et al. Attenuation of allergic contact dermatitis through the endocannabinoid system. *Science.* 2007;316(5830):1494–7.
  45. Luongo L, Palazzo E, Tambaro S, et al. 1-(2',4'-Dichlorophenyl)-6-methyl-N-cyclohexylamine-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxamide, a novel CB2 agonist, alleviates neuropathic pain through functional microglial changes in mice. *Neurobiol Dis.* 2010;37(1):177–85.
  46. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-) Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci USA.* 1998;95(14):8268–73.
  47. Burstein S, Levin E, Varanelli C. Prostaglandins and cannabis. II. Inhibition of biosynthesis by the naturally occurring cannabinoids. *Biochem Pharmacol.* 1973;22(22):2905–10.
  48. Fimiani C, Liberty T, Acuirre 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(1):23–34.
  49. Stott CG, Guy GW, Wright S, Whittle BA. The effects of cannabis extracts Tetranabinex & Nabidiolox on human cyclo-oxygenase (COX) activity. Paper presented at: Symposium on the Cannabinoids, Clearwater, June 2005.
  50. Bisogno T, Hanus L, De Petrocellis L, 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(4):845–52.
  51. Russo EB, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses.* 2006;66(2):234–46.
  52. Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry.* 2008;192(4):306–7.
  53. Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology.* 2010;35(9):1879–85.
  54. Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. *Br J Psychiatry.* 2010;197(4):285–90.
  55. Malfait AM, Gallily R, Sumariwalla PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritis therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA.* 2000;97(17):9561–6.
  56. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci USA.* 2006;103(20):7895–900.
  57. McHugh D, Hu SS, Rimmerman N, et al. N-arachidonoyl glycine, an abundant endogenous lipid, potently drives directed cellular migration through GPR18, the putative abnormal cannabinoid receptor. *BMC Neurosci.* 2010;11:44.
  58. Dmitrieva N, Nagabukuro H, Resuehr D, et al. Endocannabinoid involvement in endometriosis. *Pain.* 2010;151(3):703–10.
  59. Izzo AA, Camilleri M. Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. *Gut.* 2008;57(8):1140–55.
  60. Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. *Pharmacol Ther.* 2010;126(1):21–38.
  61. Shen M, Piser TM, Seybold VS, Thayer SA. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *J Neurosci.* 1996;16(14):4322–34.
  62. 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 21:41–4.
  63. Russo EB. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuroendocrinol Lett.* 2004;25(1–2):31–9.
  64. Russo E. Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. *Pain.* 1998;76(1–2):3–8.
  65. Spadone C. Neurophysiologie du cannabis [neurophysiology of cannabis]. *Encéphale.* 1991;17(1):17–22.
  66. Akerman S, Holland PR, Goadsby PJ. Cannabinoid (CB1) receptor activation inhibits trigeminovascular neurons. *J Pharmacol Exp Ther.* 2007;320(1):64–71.
  67. Akerman S, Kaube H, Goadsby PJ. Anandamide is able to inhibit trigeminal neurons using an in vivo model of trigeminovascular-mediated nociception. *J Pharmacol Exp Ther.* 2003;309(1):56–63.
  68. Akerman S, Kaube H, Goadsby PJ. Anandamide acts as a vasodilator of dural blood vessels in vivo by activating TRPV1 receptors. *Br J Pharmacol.* 2004;142:1354–60.
  69. 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(1):126–32.
  70. Cichewicz DL, Martin ZL, Smith FL, Welch SP. Enhancement of mu opioid antinociception by oral delta9-tetrahydrocannabinol: dose-response analysis and receptor identification. *J Pharmacol Exp Ther.* 1999;289(2):859–67.
  71. Cichewicz DL, Welch SP. Modulation of oral morphine antinociceptive tolerance and naloxone-precipitated withdrawal signs by oral delta 9-tetrahydrocannabinol. *J Pharmacol Exp Ther.* 2003;305(3):812–7.
  72. Cichewicz DL, McCarthy EA. Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. *J Pharmacol Exp Ther.* 2003;304(3):1010–5.
  73. Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol). *J Psychoactive Drugs.* 1998;30(2):187–96.
  74. Clermont-Gnamien S, Atlani S, Attal N, Le Mercier F, Guirimand F, Brasseur L. Utilisation thérapeutique du delta-9-tétrahydrocannabinol (dronabinol) dans les douleurs neuropathiques réfractaires. The therapeutic use of D9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain. *Presse Med.* 2002;31(39 Pt 1):1840–5.
  75. Attal N, Brasseur L, Guirimand D, Clermont-Gnamien S, Atlani S, Bouhassira D. Are oral cannabinoids safe and effective in refractory neuropathic pain? *Eur J Pain.* 2004;8(2):173–7.
  76. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ.* 2004;329(7460):253.
  77. Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ. Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. *Pain.* 2003;106(1–2):169–72.
  78. Neff GW, O'Brien CB, Reddy KR, et al. Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. *Am J Gastroenterol.* 2002;97(8):2117–9.

79. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain*. 2008;9(3):254–64.
80. Toth C, Au S. A prospective identification of neuropathic pain in specific chronic polyneuropathy syndromes and response to pharmacological therapy. *Pain*. 2008;138(3):657–66.
81. Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. *Am J Phys Med Rehabil*. 2010;89(10):840–8.
82. Lemberger L, Rubin A, Wolen R, et al. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. *Cancer Treat Rev*. 1982;9(Suppl B):17–23.
83. Notcutt W, Price M, Chapman G. Clinical experience with nabilone for chronic pain. *Pharm Sci*. 1997;3:551–5.
84. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. *Pain Med*. 2006;7(1):25–9.
85. Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain: Les effets de la nabilone, un cannabinoïde synthétique, sur la douleur postopératoire. *Can J Anaesth*. 2006;53(8):769–75.
86. Maida V. The synthetic cannabinoid nabilone improves pain and symptom management in cancer patients. *Breast Cancer Res Treat*. 2007;103(Part 1):121–2.
87. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *J Neurol*. 2006;253(10):1337–41.
88. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*. 2008;336(7637):199–201.
89. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain*. 2008;9(2):164–73.
90. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg*. 2010;110(2):604–10.
91. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. *Pain Pract*. 2011;11:353–68. Epub 2010 Nov 18.
92. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA*. 2003;290(13):1757–62.
93. Dyson A, Peacock M, Chen A, et al. Antihyperalgesic properties of the cannabinoid CT-3 in chronic neuropathic and inflammatory pain states in the rat. *Pain*. 2005;116(1–2):129–37.
94. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68(7):515–21.
95. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9(6):506–21.
96. Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology*. 2007;107(5):785–96.
97. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672–80.
98. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010;182(14):E694–701.
99. Wade DT, Makela PM, House H, Bateman C, Robson PJ. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler*. 2006;12:639–45.
100. Tashkin DP. Smoked marijuana as a cause of lung injury. *Monaldi Arch Chest Dis*. 2005;63(2):93–100.
101. Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. *Am J Respir Crit Care Med*. 1997;155(1):141–8.
102. Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2006;15(10):1829–34.
103. Grinspoon L, Bakalar JB. Marijuana, the forbidden medicine. Rev. and exp. edn. New Haven: Yale University Press; 1997.
104. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol*. 2008;21(2):494–502.
105. Singh R, Sandhu J, Kaur B, et al. Evaluation of the DNA damaging potential of cannabis cigarette smoke by the determination of acetaldehyde derived N2-ethyl-2'-deoxyguanosine adducts. *Chem Res Toxicol*. 2009;22(6):1181–8.
106. Joy JE, Watson SJ, Benson Jr JA. Marijuana and medicine: assessing the science base. Washington D.C.: Institute of Medicine; 1999.
107. Gieringer D. Marijuana waterpipe and vaporizer study. *MAPS Bull*. 1996;6(3):59–66.
108. Gieringer D. Cannabis “vaporization”: a promising strategy for smoke harm reduction. *J Cannabis Ther*. 2001;1(3–4):153–70.
109. Storz M, Russo EB. An interview with Markus Storz. *J Cannabis Ther*. 2003;3(1):67–78.
110. Gieringer D, St. Laurent J, Goodrich S. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. *J Cannabis Ther*. 2004;4(1):7–27.
111. Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R. Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. *J Pharm Sci*. 2006;95(6):1308–17.
112. Van der Kooy F, Pomahacova B, Verpoorte R. Cannabis smoke condensate I: the effect of different preparation methods on tetrahydrocannabinol levels. *Inhal Toxicol*. 2008;20(9):801–4.
113. Bloor RN, Wang TS, Spanel P, Smith D. Ammonia release from heated ‘street’ cannabis leaf and its potential toxic effects on cannabis users. *Addiction*. 2008;103(10):1671–7.
114. Zuurman L, Roy C, Schoemaker RC, et al. Effect of intrapulmonary tetrahydrocannabinol administration in humans. *J Psychopharmacol (Oxford, England)*. 2008;22(7):707–16.
115. Pomahacova B, Van der Kooy F, Verpoorte R. Cannabis smoke condensate III: the cannabinoid content of vaporised *Cannabis sativa*. *Inhal Toxicol*. 2009;21(13):1108–12.
116. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther*. 2007;82(5):572–8.
117. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clinical pharmacology and therapeutics*. 2011;90(6):844–51.
118. Earleywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users who vaporize. *Harm Reduct J*. 2007;4:11.
119. Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet*. 2003;362(9395):1517–26.
120. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry*. 2005;76(12):1664–9.
121. Ernst G, Denke C, Reif M, Schnelle M, Hagmeister H. Standardized cannabis extract in the treatment of postherpetic neuralgia: a randomized, double-blind, placebo-controlled cross-over study. Paper presented at: international association for cannabis as medicine, Leiden, 9 Sept 2005.
122. Holdcroft A, Maze M, Dore C, Tebbs S, Thompson S. A multicenter dose-escalation study of the analgesic and adverse effects

- of an oral cannabis extract (Cannador) for postoperative pain management. *Anesthesiology*. 2006;104(5):1040–6.
123. McPartland JM, Russo EB. Cannabis and cannabis extracts: greater than the sum of their parts? *J Cannabis Ther*. 2001; 1(3–4):103–32.
  124. de Meijer E. The breeding of cannabis cultivars for pharmaceutical end uses. In: Guy GW, Whittle BA, Robson P, editors. *Medicinal uses of cannabis and cannabinoids*. London: Pharmaceutical Press; 2004. p. 55–70.
  125. Guy GW, Robson P. A phase I, double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers (GWPK02125). *J Cannabis Ther*. 2003;3(4):121–52.
  126. Karschner EL, Darwin WD, McMahon RP, et al. Subjective and physiological effects after controlled Sativex and oral THC administration. *Clin Pharmacol Ther*. 2011;89(3):400–7.
  127. Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration. *Clin Chem*. 2011;57(1):66–75.
  128. Russo EB, Etges T, Stott CG. Comprehensive adverse event profile of Sativex. 18th annual symposium on the cannabinoids. Vol Aviemore, Scotland: International Cannabinoid Research Society; 2008. p. 136.
  129. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. *Expert Opin Pharmacother*. 2006;7(5):607–15.
  130. Pérez J. Combined cannabinoid therapy via na oromucosal spray. *Drugs Today*. 2006;42(8):495–501.
  131. 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. *Clin Rehabil*. 2003;17:18–26.
  132. Notcutt W, Price M, Miller R, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 “N of 1” studies. *Anaesthesia*. 2004;59:440–52.
  133. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain*. 2004;112(3):299–306.
  134. Rog DJ, Nurmiko T, Friede T, Young C. Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. *Neurology*. 2005;65(6):812–9.
  135. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133(1–3):210–20.
  136. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler*. 2004;10(4):434–41.
  137. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)*. 2006;45(1):50–2.
  138. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage*. 2010;39(2):167–79.
  139. Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem Biodivers*. 2007;4(8):1729–43.
  140. Lynch ME, Young J, Clark AJ. A case series of patients using medicinal marijuana for management of chronic pain under the Canadian Marijuana Medical Access Regulations. *J Pain Symptom Manage*. 2006;32(5):497–501.
  141. Janse AFC, Breekveldt-Postma NS, Erkens JA, Herings RMC. *Medicinal gebruik van cannabis: PHARMO instituut*. Institute for Drug Outcomes Research; 2004.
  142. Gorter RW, Butorac M, Cobian EP, van der Sluis W. Medical use of cannabis in the Netherlands. *Neurology*. 2005;64(5):917–9.
  143. Fitzgerald GA. Coxibs and cardiovascular disease. *N Engl J Med*. 2004;10:6.
  144. Topol EJ. Failing the public health – rofecoxib, Merck, and the FDA. *N Engl J Med*. 2004;10:6.
  145. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327–60.
  146. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *J Anal Toxicol*. 1992;16(5): 276–82.
  147. Wright S. GWMS001 and GWMS0106: maintenance of blinding. London: GW Pharmaceuticals; 2005.
  148. Clark P, Altman D. Assessment of blinding in phase III Sativex spasticity studies. GW Pharmaceuticals; 2006.
  149. Samaha AN, Robinson TE. Why does the rapid delivery of drugs to the brain promote addiction? *Trends Pharmacol Sci*. 2005;26(2):82–7.
  150. Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. *Ann N Y Acad Sci*. 1976;282:221–39.
  151. Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry*. 2004;161(11):1967–77.
  152. Smith NT. A review of the published literature into cannabis withdrawal symptoms in human users. *Addiction*. 2002;97(6): 621–32.
  153. Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA*. 2002;287(9):1123–31.
  154. Schoedel KA, Chen N, Hilliard A, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the abuse potential of nabiximols oromucosal spray in subjects with a history of recreational cannabis use. *Hum Psychopharmacol*. 2011;26:224–36.
  155. Russo EB, Mathre ML, Byrne A, et al. Chronic cannabis use in the Compassionate Use Investigational New Drug Program: an examination of benefits and adverse effects of legal clinical cannabis. *J Cannabis Ther*. 2002;2(1):3–57.
  156. Friede E, Russo EB. Neuropsychiatry: schizophrenia, depression, and anxiety. In: Onaivi E, Sugiura T, Di Marzo V, editors. *Endocannabinoids: the brain and body’s marijuana and beyond*. Boca Raton: Taylor & Francis; 2006. p. 371–82.
  157. Aragona M, Onesti E, Tomassini V, et al. Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. *Clin Neuropharmacol*. 2009;32(1):41–7.
  158. Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend*. 2003;71(1):37–48.
  159. Macleod J, Davey Smith G, Hickman M. Does cannabis use cause schizophrenia? *Lancet*. 2006;367(9516):1055.
  160. Macleod J, Hickman M. How ideology shapes the evidence and the policy: what do we know about cannabis use and what should we do? *Addiction*. 2010;105:1326–30.
  161. Hickman M, Vickerman P, Macleod J, et al. If cannabis caused schizophrenia—how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. *Addiction*. 2009;104(11):1856–61.



162. Zuardi AW, Guimaraes FS. Cannabidiol as an anxiolytic and antipsychotic. In: Mathre ML, editor. Cannabis in medical practice: a legal, historical and pharmacological overview of the therapeutic use of marijuana. Jefferson: McFarland; 1997. p. 133–41.
163. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 2011;163:1344–64.
164. Cabral G. Immune system. In: Grotenhermen F, Russo EB, editors. Cannabis and cannabinoids: pharmacology, toxicology and therapeutic potential. Binghamton: Haworth Press; 2001. p. 279–87.
165. Katona S, Kaminski E, Sanders H, Zajicek J. Cannabinoid influence on cytokine profile in multiple sclerosis. *Clin Exp Immunol*. 2005;140(3):580–5.
166. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection. A randomized, placebo-controlled clinical trial. *Ann Intern Med*. 2003;139:258–66.
167. Stott CG, Guy GW, Wright S, Whittle BA. The effects of cannabis extracts Tetranabinex and Nabidiolex on human cytochrome P450-mediated metabolism. Paper presented at: Symposium on the Cannabinoids, Clearwater, 27 June 2005.
168. Stott CG, Ayerakwa L, Wright S, Guy G. Lack of human cytochrome P450 induction by Sativex. 17th annual symposium on the cannabinoids. Saint-Sauveur, Quebec: International Cannabinoid Research Society; 2007. p. 211.
169. Grotenhermen F, Leson G, Berghaus G, et al. Developing limits for driving under cannabis. *Addiction*. 2007;102(12):1910–7.
170. Hohmann AG, Suplita 2nd RL. Endocannabinoid mechanisms of pain modulation. *AAPS J*. 2006;8(4):E693–708.
171. Clapper JR, Moreno-Sanz G, Russo R, et al. Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. *Nat Neurosci*. 2010;13:1265–70.
172. Schlosburg JE, Blankman JL, Long JZ, et al. Chronic monoacylglycerol lipase blockade causes functional antagonism of the endocannabinoid system. *Nat Neurosci*. 2010;13(9):1113–9.
173. Yu XH, Cao CQ, Martino G, et al. A peripherally restricted cannabinoid receptor agonist produces robust anti-nociceptive effects in rodent models of inflammatory and neuropathic pain. *Pain*. 2010;151(2):337–44.
174. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychoactive plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci*. 2009;30(10):515–27.
175. Wirth PW, Watson ES, ElSohly M, Turner CE, Murphy JC. Anti-inflammatory properties of cannabichromene. *Life Sci*. 1980;26(23):1991–5.
176. Davis WM, Hatoum NS. Neurobehavioral actions of cannabichromene and interactions with delta 9-tetrahydrocannabinol. *Gen Pharmacol*. 1983;14(2):247–52.
177. Ligresti A, Moriello AS, Starowicz K, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther*. 2006;318(3):1375–87.
178. De Petrocellis L, Starowicz K, Moriello AS, Vivese M, Orlando P, Di Marzo V. Regulation of transient receptor potential channels of melastatin type 8 (TRPM8): effect of cAMP, cannabinoid CB(1) receptors and endovanilloids. *Exp Cell Res*. 2007;313(9):1911–20.
179. Gauson LA, Stevenson LA, Thomas A, Baillie GL, Ross RA, Pertwee RG. Cannabigerol behaves as a partial agonist at both CB1 and CB2 receptors. 17th annual symposium on the cannabinoids. Vol Saint-Sauveur, Quebec: International Cannabinoid Research Society; 2007. p. 206.
180. Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. *Br J Pharmacol*. 2010;159(1):129–41.
181. Banerjee SP, Snyder SH, Mechoulam R. Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. *J Pharmacol Exp Ther*. 1975;194(1):74–81.
182. Evans FJ. Cannabinoids: the separation of central from peripheral effects on a structural basis. *Planta Med*. 1991;57(7):S60–7.
183. Evans AT, Formukong E, Evans FJ. Activation of phospholipase A2 by cannabinoids. Lack of correlation with CNS effects. *FEBS Lett*. 1987;211(2):119–22.
184. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153(2):199–215.
185. Hill AJ, Weston SE, Jones NA, et al. Delta-tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. *Epilepsia*. 2010;51(8):1522–32.
186. Bolognini D, Costa B, Maione S, et al. The plant cannabinoid delta9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. *Br J Pharmacol*. 2010;160(3):677–87.
187. Mehmedic Z, Chandra S, Slade D, et al. Potency trends of delta(9)-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *J Forensic Sci*. 2010;55:1209–17.
188. King LA, Carpentier C, Griffiths P. Cannabis potency in Europe. *Addiction*. 2005;100(7):884–6.
189. Potter DJ, Clark P, Brown MB. Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. *J Forensic Sci*. 2008;53(1):90–4.
190. Potter D. Growth and morphology of medicinal cannabis. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 17–54.
191. Rao VS, Menezes AM, Viana GS. Effect of myrcene on nociception in mice. *J Pharm Pharmacol*. 1990;42(12):877–8.
192. Lorenzetti BB, Souza GE, Sarti SJ, Santos Filho D, Ferreira SH. Myrcene mimics the peripheral analgesic activity of lemongrass tea. *J Ethnopharmacol*. 1991;34(1):43–8.
193. Basile AC, Sertie JA, Freitas PC, Zanini AC. Anti-inflammatory activity of oleoresin from Brazilian *Copaifera*. *J Ethnopharmacol*. 1988;22(1):101–9.
194. Tambe Y, Tsujiuchi H, Honda G, Ikeshiro Y, Tanaka S. Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, beta-caryophyllene. *Planta Med*. 1996;62(5):469–70.
195. Gertsch J, Leonti M, Raduner S, et al. Beta-caryophyllene is a dietary cannabinoid. *Proc Natl Acad Sci USA*. 2008;105(26):9099–104.
197. Gil ML, Jimenez J, Ocete MA, Zarzuelo A, Cabo MM. Comparative study of different essential oils of *Bupleurum gibraltaricum* Lamarck. *Pharmazie*. 1989;44(4):284–7.
198. Re L, Barocci S, Sonnino S, et al. Linalool modifies the nicotinic receptor-ion channel kinetics at the mouse neuromuscular junction. *Pharmacol Res*. 2000;42(2):177–82.
199. Gregg, L.C., Jung, K.M., Spradley, J.M., Nyilas, R., Suplita II, R.L., Zimmer, A., Watanabe, M., Mackie, K., Katona, I., Piomelli, D. and Hohmann, A.G. (2012) Activation of type-5 metabotropic glutamate receptors and diacylglycerol lipase-alpha initiates 2-arachidonoylglycerol formation and endocannabinoid-mediated analgesia in vivo. *The Journal of Neuroscience*, in press [DOI:10.1523/JNEUROSCI.0013-12.2012].
200. Kavia R, De Ridder D, Constantinescu C, Stott C, Fowler C. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. *Mult Scler*. 2010;16(11):1349–59.
201. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain*. 2012;13(5):438–49.
202. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clinical pharmacology and therapeutics*. 2011;90(6):844–51.