

Cannabinoids and Pain Relief

A Literature Review
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Introduction:

Pain relief (analgesia) or decreased pain sensitivity (antinociception) are among the most commonly-cited therapeutic effects of smoking cannabis. Although cannabis products have been used for thousands of years to treat pain and other conditions, it was not until the discovery of the 'cannabis receptor' in the late 1980s that modern medicine started to take cannabis seriously. The past decade has seen an explosion of research into cannabinoid metabolism, with at least two types of receptors (CB1 in the brain and spinal cord, and CB2 in the peripheral tissues) identified, and a number of endogenous ligands (endocannabinoids), the best known of which is anandamide. Pharmaceutical research is developing apace, with discovery of a number of substances (synthetic cannabinoids) which both bind to the receptors producing an effect (agonists) and block receptors preventing any effect (antagonists).

Research has moved on from asking 'whether' – i.e. do cannabinoids produce analgesia – there is now overwhelming evidence of this, through the 'how' – via receptor-mediated regulation of pain thresholds in the peripheral and spinal tissues, towards the question of how to produce analgesia more effectively, and the further questions arising from these discoveries. The 'Holy Grail' of cannabinoid research is to develop a drug which specifically targets the pain mechanisms, but does not produce the psychotropic effects (the 'high') from THC. Discovery of the endocannabinoid system has revolutionised pain research, and led to greater understanding of brain and spinal function.

One of the first modern reviews of the use of cannabis as an analgesic (pain relief) agent was undertaken by Professor Rafael Mechoulam[1]. A number of researchers using Δ^9 *THC* injections in mice, with dosages of 5-80 mg/kg, have observed significant antinociceptive (pain relieving) activity against thermal, mechanical, electrical and chemical stimuli. In some cases the effect of cannabinoids was stronger than with opioid preparations, and other researchers noted a flat response curve (i.e. once the effective dose level is reached, further dose increases cause no additional effect). Other researchers have found cannabis to potentiate the analgesic effects of opiates[2]. Significant analgesia has been produced in animals with injections into the brain stem and spinal cord.[3] [4]

The dosages required to produce detectable pain relief in animal models were substantially in excess of dosages encountered in normal social use (typically

1 Mechoulam R. (1986) Cannabinoids as Therapeutic Agents. Boca Raton Fla. CRC Press pp108-120
2 Welch SP & Stevens DL (1992) Antinociceptive activity of intrathecally administered cannabinoids, alone and in combination with morphine, in mice. J Pharmacol Exper Ther 262 pp10-18.
3 Lichtman AH & Martin BR (1991) Spinal and supraspinal components of cannabinoid-induced antinociception. J Pharmacol Exper Ther 258 pp517-523.
4 Martin WJ et al (1993) Antinociceptive actions of cannabinoids following intraventricular administration in rats. Brain Research 629 pp300-304.

0.1-1.0 mg/kg). The effective dose of THC in the early mouse studies (approx. 5mg/kg) would be the equivalent of an average 70kg man consuming 350mg THC, or smoking 10 grams of cannabis with a potency of 3.5%. However in most clinical trials of cannabis-extracts, dosages have generally been much lower than would be encountered in typical social use.

The following sections provide detailed reviews and citations from original scientific papers, including anecdotal evidence, animal and receptor studies, human studies including clinical trials, and learned reviews.

Anecdotal Evidence, Surveys & Patient Reports

Many new leads for medical research have arisen from reports of cannabis users as to how the drug has affected their condition. Such reports must be treated with caution as the effects described might be due to placebo-effects or increased general feelings of well-being. However the results of surveys, particularly where a number of patients report similar symptoms, provide an early warning of potential effects and side-effects of cannabis and cannabinoids.

In Judge Young's report[5] numerous cases histories were described outlining the use of cannabis to reduce muscle tension (spasticity) in individuals with multiple sclerosis or spinal injury. The potential efficacy of cannabis in treatment of MS is increasingly accepted by patients and medical practitioners alike. Gill & Williams[6], in a preliminary study of attitudes to cannabis-based medicine among 67 chronic pain patients in the UK, found "*Fifty-two percent of patients were doubtful about taking cannabinoids: unwillingness was strongly associated with specific concerns about side effects, addiction, tolerance, and losing control but not with general beliefs about medication or personal or medical variables other than age*" In a similar German study of 128 patients, Schnelle et al[7] found "*The most frequently mentioned indications for medicinal cannabis use were depression (12.0%), multiple sclerosis (10.8%), HIV-infection (9.0%), migraine (6.6%), asthma (6.0%), back pain (5.4%), hepatitis C (4. 8%), sleeping disorders (4.8%), epilepsy (3.6%), spasticity (3.6%), headache (3.6%), alcoholism (3.0%), glaucoma (3.0%), nausea (3.0%), disk prolapse (2.4%), and spinal cord injury (2.4%)... 72.2% of the patients stated the symptoms of their illness to have 'much improved' after cannabis ingestion, 23.4% stated to have 'slightly improved', 4.8% experienced 'no change' and 1.6% described that their symptoms got 'worse'... 60.8% stated (themselves) to be 'very satisfied', 24.0% 'satisfied', 11.2% 'partly satisfied' and 4.0% were 'not satisfied'. 70.8% experienced no side effects, 26.4% described 'moderate' and 3.3% 'strong' side effects*."

A study of 50 medicinal- cannabis using patients in Canada by Ogborne et al[8] found "*They reported using cannabis for a variety of conditions including HIV-AIDS-related problems, chronic pain, depression, anxiety, menstrual cramps, migraine, narcotic addiction as well as everyday aches, pains, stresses and sleeping difficulties*." Fishbain et al[9] found a significant minority of chronic pain patients in the USA used cannabis but were unwilling to admit this to their doctors or researchers. Mechoulam[10] noted "*Illegally... smoking marijuana... is used for ameliorating the*

5 Young FL (1988) op cit.

6 Gill A, Williams AC. [2001] Preliminary study of chronic pain patients' concerns about cannabinoids as analgesics. Clin J Pain 17(3):245-8

7 Schnelle M, Grotenhermen F, Reif M, Gorter RW [1999] [Results of a standardized survey on the medical use of cannabis products in the German-speaking area].[Article in German] Forsch Komplementarmed 6 Suppl 3:28-36

8 Ogborne AC, Smart RG, Weber T, Birchmore-Timney C [2000] Who is using cannabis as a medicine and why: an exploratory study. J Psychoactive Drugs 2000 Oct-Dec;32(4):435-43

9 Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS [1999] Validity of self-reported drug use in chronic pain patients. Clin J Pain 15(3):184-91

10 Mechoulam R. [1999] Recent advantages in cannabinoid research. Forsch Komplementarmed 6 Suppl 3:16-20

symptoms of multiple sclerosis, against pain, and in a variety of other diseases." Ware et al[11] studied 15 patients who claimed to use herbal cannabis for therapeutic reasons, noting "*Twelve patients reported improvement in pain and mood, while 11 reported improvement in sleep. Eight patients reported a 'high'; six denied a 'high'. Tolerance to cannabis was not reported*" and concluded "*Small doses of smoked cannabis may improve pain, mood and sleep in some patients with chronic pain*." Following a larger Canadian survey, Ware et al[12] concluded "*cannabis use is prevalent among the chronic non-cancer pain population, for a wide range of symptoms, with considerable variability in the amounts used*." Page et al[13] reported a survey of MS patients in Western Canada "*Symptoms reported to be ameliorated included anxiety/depression, spasticity and chronic pain.*". Clark et al[14] found "*Medical cannabis use was associated with male gender, tobacco use, and recreational cannabis use. The symptoms reported by medical cannabis users to be most effectively relieved were stress, sleep, mood, stiffness/spasm, and pain*" Swift et al[15], found among Australian medical users "*Long term and regular medical cannabis use was frequently reported for multiple medical conditions including chronic pain (57%), depression (56%), arthritis (35%), persistent nausea (27%) and weight loss (26%). Cannabis was perceived to provide "great relief" overall (86%), and substantial relief of specific symptoms such as pain, nausea and insomnia. It was also typically perceived as superior to other medications in terms of undesirable effects, and the extent of relief provided*." In a survey of Amyotrophic Lateral Sclerosis (ALS) patients using cannabis Amtmann et al[16] reported "*cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling. Cannabis was reported ineffective in reducing difficulties with speech and swallowing, and sexual dysfunction. The longest relief was reported for depression (approximately two to three hours).*"

A survey of patients using smoked cannabis in the Netherlands by Gorter et al[17] found "*A majority (64.1%) of patients reported a good or excellent effect on their symptoms. Of these patients, approximately 44% used cannabis for >/=5 months. Indications were neurologic disorders, pain, musculoskeletal disorders, and cancer anorexia/cachexia. Inhaled cannabis was perceived as more effective than oral administration. Reported side effects were generally mild.*" In a similar study, Erkens et al[18] noted "*Of all patients, 42% suffered from multiple sclerosis, 11% suffered from rheumatic diseases, and 60% of respondents already used cannabis before the legalization. Cannabis was mainly used for chronic pain and muscle cramp/stiffness.The indication of medicinal cannabis use was in accordance with the labeled indications*."

Ware et al[19] conducted a survey of UK cannabis patients, reporting "*Medicinal cannabis use was reported by patients with chronic pain (25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (19%). Medicinal cannabis use was associated with younger age, male gender and previous recreational use ($p < 0.001$).*" In a survey

11 Ware MA, Gamsa A, Persson J, Fitzcharles MA. [2002] Cannabis for chronic pain: case series and implications for clinicians. Pain Res Manag. 7(2):95-9.

12 Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. [2003] Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain. 102(1-2):211-6.

13 Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC. [2003] Cannabis use as described by people with multiple sclerosis. Can J Neurol Sci. 30(3):201-5.

14 Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. [2004] Patterns of cannabis use among patients with multiple sclerosis. Neurology. 62(11):2098-100.

15 Swift W, Gates P, Dillon P. [2005] Survey of Australians using cannabis for medical purposes. Harm Reduct J. 2:18.

16 Amtmann D, Weydt P, Johnson KL, Jensen MP, Carter GT. [2004] Survey of cannabis use in patients with amyotrophic lateral sclerosis. Am J Hosp Palliat Care. 21(2):95-104.

17 Gorter RW, Butorac M, Cobian EP, van der Sluis W. [2005] Medical use of cannabis in the Netherlands. Neurology. 64(5):917-9.

18 Erkens JA, Janse AF, Herings RM. [2005] Limited use of medicinal cannabis but for labeled indications after legalization. Pharmacoepidemiol Drug Saf. 14(11):821-2.

19 Ware MA, Adams H, Guy GW. [2005] The medicinal use of cannabis in the UK: results of a nationwide survey. Int J Clin Pract. 59(3):291-5.

of UK Aids patients, Woolridge et al[20] reported "*Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), anxiety (93%), nerve pain (90%), depression (86%), and paresthesia (85%). Many cannabis users (47%) reported associated memory deterioration. Symptom control using cannabis is widespread in HIV outpatients. A large number of patients reported that cannabis improved symptom control*" A further survey of sickle-cell disease sufferers by Howard et al[21] noted "*The main reasons for use were to reduce pain in 52%, and to induce relaxation or relieve anxiety and depression in 39%.*"

The 1994 IDMU study of cannabis users[22] asked respondents to report any physical or mental health problems and/or benefits which they attributed to cannabis use. Thirty two individuals cited "pain relief" as the main benefit they received, the fourth most common benefit reported (after relaxation (n=89), stress relief (n=67) and improvements in personal development and outlook (n=36)). Two individuals specifically mentioned use of cannabis as a muscle relaxant.

Animal Studies

The discovery of endocannabinoids and receptor types have opened up a field of research into potential drugs based on anandamide and other endocannabinoids[23]. Antagonists (blockers) of the cannabinoid receptors have been shown to increase sensitivity to pain in laboratory animals.

Meng et al[24] reported the analgesic activity of the cannabinoids to result from a brainstem circuit (rostral ventromedial medulla - RVM) which also contributes to the action of morphine, but in a pharmacologically different manner from morphine. They claimed that increasing or decreasing levels endogenous cannabinoids (e.g. anandaminde) would normally regulate pain thresholds through modulation of RVM activity, and concluded: "*analgesia produced by cannabinoids and opioids involves similar brainstem circuitry and that cannabinoids are indeed centrally acting analgesics with a new mechanism of action.*" Meng & Johansen[25] noted "*cannabinoids act directly within the RVM to affect off-cell activity, providing one mechanism by which cannabinoids produce antinociception*" de Novellis et al[26] reported "*s.c. injection of formalin modifies RVM neuronal activities and this effect is prevented by PAG cannabinoid receptor stimulation. Moreover, the physiological stimulation of PAG mGlu5, but not mGlu1 glutamate receptors, seems to be required for the cannabinoid-mediated effect.*"

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20 Woolridge E, Barton S, Samuel J, Osorio J, Dougherty A, Holdcroft A. [2005] Cannabis use in HIV for pain and other medical symptoms. J Pain Symptom Manage. 29(4):358-67.

21 Howard J, Anie KA, Holdcroft A, Korn S, Davies SC. [2005] Cannabis use in sickle cell disease: a questionnaire study. Br J Haematol. 131(1):123-8.

22 Atha & Blanchard [1997] op cit.

23 Di Marzo, Bisogno T, De Petrocellis L [2000] Endocannabinoids: new targets for drug development. Curr Pharm Des 6(13):1361-80

24 I D Meng, B H Manning, W J Martin & H L Fields (1998) An analgesia circuit activated by cannabinoids (Letter to Nature) Nature 395, p381

25 Meng ID, Johansen JP. [2004] Antinociception and modulation of rostral ventromedial medulla neuronal activity by local microinfusion of a cannabinoid receptor agonist. Neuroscience. 124(3):685-93.

26 de Novellis V, Mariani L, Palazzo E, Vita D, Marabese I, Scafuro M, Rossi F, Maione S. [2005] Periaqueductal grey CB1 cannabinoid and metabotropic glutamate subtype 5 receptors modulate changes in rostral ventromedial medulla neuronal activities induced by subcutaneous formalin in the rat. Neuroscience. 134(1):269-81.

Strangman et al[27] found that pre-treatment with the cannabinoid antagonist SR141716A significantly increased the response to a noxious & painful chemical stimulus in laboratory animals, and concluded: "*endogenous cannabinoids serve naturally to modulate the maintenance of pain following repeated noxious stimulation*" Lever et al found the cannabinoid antagonist SR 141716A increased the release of the excitatory neurotransmitted substance P in response to painful stimulation, suggesting tonic CB1 receptor activity inhibits the release of excitatory neurotransmitters in response to pain. Salio et al[28] reported "*Several lines of evidence show that endogenous and exogenous cannabinoids modulate pain transmission at the spinal level through specific cannabinoid-1 (CB1) receptors*." Costa et al[29] found CB1 antagonists reversed the effects of anandamide in rats, and Martin et al[30] found SR141716A blocked CB1-mediated analgesia, however Beaulieu et al[31] failed to replicate the pain-sensitising effects of CB1 antagonists in the rat formalin test. Carta et al[32] found dopamine antagonists blocked the analgesic effects of THC in rats. Chapman[33] reported "*tonic cannabinoid CB1 receptor activation, but not CB2 receptor activation, attenuates acute nociceptive transmission, at the level of the spinal cord*" In mice, Guhring et al[34] found the CB1 cannabinoid receptor agonist HU210 showed "*higher(antinociceptive) efficacy and potency than morphine*".

In mice, Fride et al[35] reported *"(+)-Cannabidiol-DMH inhibited the peripheral pain response and arachidonic-acid-induced inflammation of the ear*." Than et al[36] reported "*an alpha2-adrenoceptor agonist or micro opioid receptor agonist when combined with a cannabinoid receptor agonist showed significant synergy in antinociception in the hot plate test. However, for the tail flick nociceptive response to heat, only cannabinoid and micro opioid receptor antinociceptive synergy was demonstrated*." Exposing mice to marijuana smoke, Varvel et al[37] found "*the acute cannabinoid effects of marijuana smoke exposure on analgesia, hypothermia, and catalepsy in mice result from delta9-THC content acting at CB1 receptors and that the non-delta9-THC constituents of marijuana (at concentrations relevant to those typically consumed) influence these effects only minimally, if at all*." Ulugol et al[38] found "*WIN 55,212-2, a cannabinoid agonist, and the NSAID ketorolac, either alone or in combination, produced dose-dependent antinociception in the writhing test. Isobolographic analysis showed additive interactions between WIN 55,212-2*

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27 Strangman NM, Patrick SL, Hohmann AG, Tsou K, Walker JM (1998) Evidence for a role of endogenous cannabinoids in the modulation of acute and tonic pain sensitivity. Brain Res 1998 Dec 7;813(2):323-8

28 Salio C, Fischer J, Franzoni MF, Conrath M. [2002] Pre- and postsynaptic localizations of the CB1 cannabinoid receptor in the dorsal horn of the rat spinal cord. Neuroscience 110(4):755-64

29 Costa B, Vailati S, Colleoni M. [1999] SR 141716A, a cannabinoid receptor antagonist, reverses the behavioural effects of anandamide-treated rats. Behav Pharmacol 1999 May;10(3):327-31

30 Martin WJ, Loo CM, Basbaum AI. [1999] Spinal cannabinoids are anti-allodynic in rats with persistent inflammation. Pain 82(2):199-205

31 Beaulieu1 P, Bisogno1 T, Punwar S, Farquhar-Smith WP, Ambrosino G, Di Marzo V, Rice AS. [2000] Role of the endogenous cannabinoid system in the formalin test of persistent pain in the rat. Eur J Pharmacol 396(2-3):85-92

32 Carta G, Gessa GL, Nava F. [1999] Dopamine D(2) receptor antagonists prevent delta(9)-tetrahydrocannabinol-induced antinociception in rats. Eur J Pharmacol 1999 Nov 19;384(2-3):153-6

33 Chapman V. [1999] The cannabinoid CB1 receptor antagonist, SR141716A, selectively facilitates nociceptive responses of dorsal horn neurones in the rat. Br J Pharmacol 127(8):1765-7

34 Guhring H, Schuster J, Hamza M, Ates M, Kotalla CE, Brune K [2001] HU-210 shows higher efficacy and potency than morphine after intrathecal administration in the mouse formalin test. Eur J Pharmacol 429(1-3):127-34

35 Fride E, Feigin C, Ponde DE, Breuer A, Hanus L, Arshavsky N, Mechoulam R. [2004] (+)-Cannabidiol analogues which bind cannabinoid receptors but exert peripheral activity only. Eur J Pharmacol. 506(2):179-88.

36 Tham SM, Angus JA, Tudor EM, Wright CE. [2004] Synergistic and additive interactions of the cannabinoid agonist CP55,940 with {micro} opioid receptor and {alpha}2-adrenoceptor agonists in acute pain models in mice. Br J Pharmacol. 144(6):875-84

37 Varvel SA, Bridgen DT, Tao Q, Thomas BF, Martin BR, Lichtman AH. [2005] Delta9-tetrahydrocannbinol accounts for the antinociceptive, hypothermic, and cataleptic effects of marijuana in mice. J Pharmacol Exp Ther. 314(1):329-37.

38 Ulugol A, Ozyigit F, Yesilyurt O, Dogrul A. [2006] The additive antinociceptive interaction between WIN 55,212-2, a cannabinoid agonist, and ketorolac. Anesth Analg. 102(2):443-7.

and ketorolac when they were coadministered systemically." and concluded "*The combination of cannabinoids and NSAIDs may have utility in the pharmacotherapy of pain*."

Studying the relationship between endocannabinoids and spinal fos proteins in rats, Nackley et al[39] reported "*These data provide direct evidence that a peripheral cannabinoid mechanism suppresses the development of inflammation-evoked neuronal activity at the level of the spinal dorsal horn and implicate a role for CB(2) and CB(1) in peripheral cannabinoid modulation of inflammatory nociception*." Finn et al[40], investigating the role of the periaqueductal grey matter in the rat, postulated "*a role for the PAG in both cannabinoid-mediated anti-nociceptive and anti-aversive responses*." and noted[41] "*These data suggest an important role for the CB(1) receptor in mediating fear-conditioned analgesia and provide evidence for differential modulation of conditioned aversive behaviour by CB(1) receptors during tonic, persistent pain*."

Studying the interaction of cannabinoids and NSAID drugs in mice, Anikwue et al[42] noted "*In animals given chronic Delta(9)-THC, only diclofenac and acetaminophen (paracetamol) were active*", Ates et al[43] observed "*endocannabinoids play a major role in mediating flurbiprofen-induced antinociception at the spinal level*." In rats, Ottani et al[44] found "*the analgesic effect of paracetamol is prevented by two antagonists at cannabinoid CB1 receptors (AM281 and SR141716A) at doses that prevent the analgesic activity of the cannabinoid CB1 agonist HU210*." Guindon & Beaulieu[45] noted "*locally injected anandamide, ibuprofen, rofecoxib and their combinations decreased pain behavior in neuropathic animals. Local use of endocannabinoids to treat neuropathic pain may be an interesting way to treat this condition without having the deleterious central effects of systemic cannabinoids*." Guindon et al[46] later reported "*The combination of anandamide with ibuprofen produced synergistic antinociceptive effects involving both cannabinoid CB(1) and CB(2) receptors*." Investigating interactions between analgesic activities of cannabis and cocaine, Forman[47] reported "*These findings suggest that activation of the CB1 receptor participates significantly in antinociception resulting from treatment with cocaine*" Helyes et al[48] found cannabinoid blockers increased pain perception in rats "*Both SR141716A and SR144528 increased hyperalgesia, indicating that endogenous cannabinoids acting on CB(1) and peripheral CB(2)-like receptors play substantial role in neuropathic conditions to diminish hyperalgesia."*

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39 Nackley AG, Suplita RL 2nd, Hohmann AG. [2003] A peripheral cannabinoid mechanism suppresses spinal fos protein expression and pain behavior in a rat model of inflammation. Neuroscience. 117(3):659-70.

40 Finn DP, Jhaveri MD, Beckett SR, Roe CH, Kendall DA, Marsden CA, Chapman V. [2003] Effects of direct periaqueductal grey administration of a cannabinoid receptor agonist on nociceptive and aversive responses in rats. Neuropharmacology. 45(5):594-604.

41 Finn DP, Beckett SR, Richardson D, Kendall DA, Marsden CA, Chapman V. [2004] Evidence for differential modulation of conditioned aversion and fear-conditioned analgesia by CB1 receptors. Eur J Neurosci. 20(3):848-52.

42 Anikwue R, Huffman JW, Martin ZL, Welch SP. [2002] Decrease in efficacy and potency of nonsteroidal anti-inflammatory drugs by chronic delta(9)-tetrahydrocannabinol administration. J Pharmacol Exp Ther. 303(1):340-6.

43 Ates M, Hamza M, Seidel K, Kotalla CE, Ledent C, Guhring H. [2003] Intrathecally applied flurbiprofen produces an endocannabinoid-dependent antinociception in the rat formalin test. Eur J Neurosci. 17(3):597-604.

44 Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. [2006] The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. Eur J Pharmacol. 531(1-3):280-1.

45 Guindon J, Beaulieu P. [2006] Antihyperalgesic effects of local injections of anandamide, ibuprofen, rofecoxib and their combinations in a model of neuropathic pain. Neuropharmacology. Jan 23; [Epub ahead of print]

46 Guindon J, De Lean A, Beaulieu P. [2006] Local interactions between anandamide, an endocannabinoid, and ibuprofen, a nonsteroidal anti-inflammatory drug, in acute and inflammatory pain. Pain. 121(1-2):85-93.

47 Forman LJ. [2003] The effect of cannabinoid receptor antagonism with SR141716A on antinociception induced by cocaine and the NMDA receptor antagonist, MK-801. Brain Res Bull. 61(2):153-8

48 Helyes Z, Nemeth J, Than M, Bolcskei K, Pinter E, Szolcsanyi J. [2003] Inhibitory effect of anandamide on resiniferatoxin-induced sensory neuropeptide release in vivo and neuropathic hyperalgesia in the rat. Life Sci. 73(18):2345-53.

Maccarone et al[49] found anandamide to stimulate platelets, an opposite action to aspirin, suggesting cannabinoids may contribute to analgesia without the effects on blood clotting or internal bleeding associated with heavy or regular aspirin use. Corchero et al[50], in a study of gene expression on receptor activity, suggested: '*a possible interaction between the cannabinoid and opioid systems in the caudate-putamen*' However Hamann et al[51] found analgesia caused by the synthetic cannabinoid Nabilone not to have an opioid receptor component. Fowler et al[52] found evidence that ibuprofen and similar drugs may act by reducing the rate at which a natural cannabinoid - anandamide - is broken down in the body.

Martin et al[53], studying the sites in the brain mediating cannabinoid analgesia, found that the cannabinoid agonist WIN55212-2 '*significantly elevated tail-flick latencies when injected into the amygdala, the lateral posterior and submedius regions of the thalamus, the superior colliculus and the noradrenergic A5 region.*' For peripheral activity, Hohmann et al[54] considered their results to '*provide anatomical evidence for presynaptic as well as postsynaptic localization of cannabinoid receptors in the spinal dorsal horn.*' In a study of spinal injury in rats, Kawasaki et al[55] concluded "*after nerve injury, opioids lose their capability to suppress C-fiber-induced spinal neuron activation in the injured L(5) but not in the intact L(4) spinal segment, whereas cannabinoids still maintain their efficacy.*"

In rats, Kelly et al[56] found "*spinal CB1 receptors modulate the transmission of C- and A delta-fiber-evoked responses in anesthetized rats; this may reflect pre- and/or postsynaptic effects of cannabinoids on nociceptive transmission. CB1 receptors inhibit synaptic release of glutamate in rat dorsolateral striatum, a similar mechanism of action may underlie the effects of ACEA on noxious evoked responses of spinal neurons reported here.*" Chapman[57] found HU210 reduced spinal pain transmission in healthy, but not nerve-damaged rats. Johanek et al[58] concluded "*cannabinoids possess antihyperalgesic properties at doses that alone do not produce antinociception, and are capable of acting at both spinal and peripheral sites*" Bridges et al[59] found the CB1 agonist WIN55,212-2 reduced hyperalgesia in neuropathic pain, and concluded "*cannabinoids may have therapeutic potential in neuropathic pain, and that this effect is mediated through the CB(1)*

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49 Maccarrone M, Bari M, Menichelli A, Del Principe D, Agro AF (1999) Anandamide activates human platelets through a pathway independent of the arachidonate cascade. FEBS Lett 447(2-3):277-82

50 Corchero J, Romero J, Berrendero F, Fernandez-Ruiz J, Ramos JA, Fuentes JA, Manzanares J (1999) Time-dependent differences of repeated administration with Delta9-tetrahydrocannabinol in proenkephalin and cannabinoid receptor gene expression and G-protein activation by mu-opioid and CB1-cannabinoid receptors in the caudate-putamen. Brain Res Mol Brain Res 67(1):148-57

51 Hamann W, di Vadi PP (1999) Analgesic effect of the cannabinoid analogue nabilone is not mediated by opioid receptors. Lancet 353(9152):560

52 Fowler CJ, Janson U, Johnson RM, Wahlstrom G, Stenstrom A, Norstrom k, Tiger G (1999) Inhibition of anandamide hydrolysis by the enantiomers of ibuprofen, ketorolac, and flurbiprofen. Arch Biochem Biophys 362(2):191-6

53 Martin WJ, Coffin PO, Attias E, Balinsky M, Tsou K, Walker JM (1999) Anatomical basis for cannabinoid-induced antinociception as revealed by intracerebral microinjections. Brain Res 822(1-2):237-42

54 Hohmann AG, Briley EM, Herkenham M (1999) Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. Brain Res 822(1-2):17-25

55 Kawasaki Y, Kohno T, Ji RR. [2006] Different effects of opioid and cannabinoid receptor agonists on C-fiber-induced extracellular signal-regulated kinase activation in dorsal horn neurons in normal and spinal nerve-ligated rats. J Pharmacol Exp Ther. 316(2):601-7.

56 Kelly S, Chapman V. [2001] Selective cannabinoid CB1 receptor activation inhibits spinal nociceptive transmission in vivo. J Neurophysiol 86(6):3061-4

57 Chapman V. [2001] Functional changes in the inhibitory effect of spinal cannabinoid (CB) receptor activation in nerve injured rats. Neuropharmacology 41(7):870-7

58 Johanek LM, Heitmiller DR, Turner M, Nader N, Hodges J, Simone DA. [2001] Cannabinoids attenuate capsaicin-evoked hyperalgesia through spinal and peripheral mechanisms. Pain 93(3):303-15

59 Bridges D, Ahmad K, Rice AS. [2001] The synthetic cannabinoid WIN55,212-2 attenuates hyperalgesia and allodynia in a rat model of neuropathic pain. Br J Pharmacol 133(4):586-94

receptor". Ross et al[60] suggested "*analgesic actions of cannabinoids may be mediated by presynaptic inhibition of transmitter release in sensory neurones*." In rats, Finn et al[61] reported "*coadministration of a low dose of morphine, but not cannabidiol, with Delta9-THC, increased antinociception and 5-hydroxytryptamine levels in the thalamus in a model of persistent nociception*". Labuda & Little[62] reported "*The robust effects of the non-selective cannabinoid receptor agonist WIN55,212-2 and morphine support reports in the literature that systemic cannabinoid receptor agonists and opioids are active in neuropathic pain.*" Cox & Welch[63] found "*Delta9-THC induces increased immunoreactive dynorphin A (idyn A) levels in nonarthritic rats while decreasing idyn A in arthritic rats. We hypothesize that the elevated idyn A level in arthritic rats contributes to hyperalgesia by interaction with N-methyl-D-aspartate receptors, and that Delta9-THC induces antinociception by decreasing idyn A release*"

Farquhar-Smith et al[64], studying bladder pain models in rats found "*Anandamide (via CB1 receptors) and palmitoylethanolamide (putatively via CB2 receptors) attenuated a referred hyperalgesia in a dose-dependent fashion. CB1 and CB2 receptors are strategically situated to influence the nerve growth factor-driven referred hyperalgesia associated with inflammation of the urinary bladder. These data implicate cannabinoids as a novel treatment for vesical pain.*". Fox et al[65] concluded "*cannabinoids are highly potent and efficacious antihyperalgesic agents in a model of neuropathic pain*". Siegling et al[66] concluded "*cannabinoid CB(1) receptor upregulation contributes to the increased analgesic efficacy of cannabinoids in chronic pain conditions*". Studying deep-tissue pain in mice, Kehl et al[67] reported "*cannabinoids differentially modulated carrageenan- and tumor-evoked hyperalgesia in terms of potency and receptor subtypes involved suggesting that differences in underlying mechanisms may exist between these two models of deep tissue pain.*" In a study of nerve injury in rats, Lim et al[68] concluded "*upregulation of spinal CB1Rs following peripheral nerve injury may contribute to the therapeutic effects of exogenous cannabinoids on neuropathic pain*" Following a study of the effects of a cannabinoid agonist in a rat model of diabetic neuropathy, Dogrul et al[69] concluded "*cannabinoids have a potential beneficial effect on experimental diabetic neuropathic pain*" Ulugol et al[70] found the CB1 agonist "*WIN 55,212-2 has an antiallodynic effect in streptozocin-induced diabetic rats and may be a promising approach in the treatment of diabetic neuropathy.*"

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60 Ross RA, Coutts AA, McFarlane SM, Anavi-Goffer S, Irving AJ, Pertwee RG, MacEwan DJ, Scott RH. [2001] Actions of cannabinoid receptor ligands on rat cultured sensory neurones: implications for antinociception. Neuropharmacology 2001;40(2):221-32

61 Finn DP, Beckett SR, Roe CH, Madjd A, Fone KC, Kendall DA, Marsden CA, Chapman V. [2004] Effects of coadministration of cannabinoids and morphine on nociceptive behaviour, brain monoamines and HPA axis activity in a rat model of persistent pain. Eur J Neurosci. 19(3):678-86.

62 LaBuda CJ, Little PJ. [2005] Pharmacological evaluation of the selective spinal nerve ligation model of neuropathic pain in the rat. J Neurosci Methods. 144(2):175-81.

63 Cox ML, Welch SP. [2004] The antinociceptive effect of Delta9-tetrahydrocannabinol in the arthritic rat. Eur J Pharmacol. 493(1-3):65-74.

64 Farquhar-Smith WP, Rice AS. [2001] Administration of endocannabinoids prevents a referred hyperalgesia associated with inflammation of the urinary bladder. Anesthesiology 2001 Mar;94(3):507-13; discussion 6A

65 Fox A, Kesingland A, Gentry C, McNair K, Patel S, Urban L, James I [2001] The role of central and peripheral Cannabinoid(1) receptors in the antihyperalgesic activity of cannabinoids in a model of neuropathic pain. Pain 2001 May;92(1-2):91-100

66 Siegling A, Hofmann HA, Denzer D, Mauler F, De Vry J [2001] Cannabinoid CB(1) receptor upregulation in a rat model of chronic neuropathic pain. Eur J Pharmacol 415(1):R5-7

67 Kehl LJ, Hamamoto DT, Wacnik PW, Croft DL, Norsted BD, Wilcox GL, Simone DA. [2003] A cannabinoid agonist differentially attenuates deep tissue hyperalgesia in animal models of cancer and inflammatory muscle pain. Pain. 103(1-2):175-86.

68 Lim G, Sung B, Ji RR, Mao J. [2003] Upregulation of spinal cannabinoid-1-receptors following nerve injury enhances the effects of Win 55,212-2 on neuropathic pain behaviors in rats. Pain. 105(1-2):275-83.

69 Dogrul A, Gul H, Yildiz O, Bilgin F, Guzeldemir ME. [2004] Cannabinoids blocks tactile allodynia in diabetic mice without attenuation of its antinociceptive effect. Neurosci Lett. 368(1):82-6.

70 Ulugol A, Karadag HC, Ipci Y, Tamer M, Dokmeci I. [2004] The effect of WIN 55,212-2, a cannabinoid agonist, on tactile allodynia in diabetic rats. Neurosci Lett. 371(2-3):167-70.

Studying the relationship between gamma-hydroxybutyric acid (GABA) and cannabinoids in rat spinal cord, Naderi et al[71] reported "*Our results confirm that intrathecal administration of cannabinoid and GABA(B) receptor agonists have analgesic effects and that spinal antinociceptive effects of GABA(B) receptor agonists are likely through endocannabinoid modulation*."

Studying the function of the amygdala in rats, Manning et al[72] reported "*The results constitute the first causal data demonstrating the necessity of descending pain-modulatory circuitry (of which the CeA is a component) for the full expression of cannabinoid-induced antinociception in the rat. Furthermore, the results complement previous findings suggesting an overlap in neural circuitry activated by opioids and cannabinoids*." Azad et al[73] concluded "*The endogenous cannabinoid system is involved in the control of neuroplasticity as part of pain processing . Cannabinoids prevent the formation of (long-term potentiation) in the amygdala via activation of CB1 receptors*." Hohmann et al[74] noted "*coordinated release of 2-AG and anandamide in the periaqueductal grey matter might mediate opioid-independent stress-induced analgesia*"

Dyson et al[75] reported "*CT-3 (ajulemic acid) is a cannabinoid receptor agonist and is efficacious in animal models of chronic pain by activation of the CB1 receptor. Whilst it shows significant cannabinoid-like CNS activity, it exhibits a superior therapeutic index compared to other cannabinoid compounds*" Mitchell et al[76] reported "*ajulemic acid reduces abnormal pain sensations associated with chronic pain without producing the motor side effects associated with THC and other non-selective cannabinoid receptor agonists*" Costa et al[77] investigating a rat model of MS, noted that the CB1 receptor agonist "*SR141716 is effective not only in alleviating neuropathic pain but also in favouring the nerve myelin repair*" Combining spinal cannabinoids and yohimbine, 2-adrenoreceptor agonist, Khodayar et al[78] concluded "*spinal cannabinoid and 2-adrenoceptor systems are able to induce antinociception in both phases of formalin test, and (2) the cannabinoid system may be involved in the antinociception induced by adrenoceptors in the early phase*." Antonoiu et al[79] investigated the behavioural effects of 1',1'-dithiolane delta8-THC analogue AMG-3, a cannabinomimetic molecule with high affinity for CB1/CB2 receptors in rats, finding "*the administration of AMG-3 to rats elicits a specific behavioral profile, most probably associated with the activation of CB1 receptors and without effects indicating abuse potential*"

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71 Naderi N, Shafaghi B, Khodayar MJ, Zarindast MR. [2005] Interaction between gamma-aminobutyric acid GABAB and cannabinoid CB1 receptors in spinal pain pathways in rat. Eur J Pharmacol. 514(2-3):159-64

72 Manning BH, Martin WJ, Meng ID. [2003] The rodent amygdala contributes to the production of cannabinoid-induced antinociception. Neuroscience. 120(4):1157-70.

73 Azad SC, Huge V, Schops P, Hilf C, Beyer A, Dodt HU, Rammes G, Zieglgansberger W. [2005] [Endogenous cannabinoid system. Effect on neuronal plasticity and pain memory] [Article in German] Schmerz. 19(6):521-7.

74 Hohmann AG, Suplita RL, Bolton NM, Neely MH, Fegley D, Mangieri R, Krey JF, Walker JM, Holmes PV, Crystal JD, Duranti A, Tontini A, Mor M, Tarzia G, Piomelli D. [2005] An endocannabinoid mechanism for stress-induced analgesia. Nature. 435(7045):1108-12.

75 Dyson A, Peacock M, Chen A, Courade JP, Yaqoob M, Groarke A, Brain C, Loong Y, Fox A. [2005] Antihyperalgesic properties of the cannabinoid CT-3 in chronic neuropathic and inflammatory pain states in the rat. Pain. 116(1-2):129-37.

76 Mitchell VA, Aslan S, Safaei R, Vaughan CW. [2005] Effect of the cannabinoid ajulemic acid on rat models of neuropathic and inflammatory pain. Neurosci Lett. 382(3):231-5.

77 Costa B, Trovato AE, Colleoni M, Giagnoni G, Zarini E, Croci T. [2005] Effect of the cannabinoid CB1 receptor antagonist, SR141716, on nociceptive response and nerve demyelination in rodents with chronic constriction injury of the sciatic nerve. Pain. 116(1-2):52-61.

78 Khodayar MJ, Shafaghi B, Naderi N, Zarrindast MR. [2006] Antinociceptive effect of spinally administered cannabinergic and 2-adrenoceptor drugs on the formalin test in rat: possible interactions. J Psychopharmacol. 20(1):67-74.

79 Antoniou K, Galanopoulos A, Vlachou S, Kourouli T, Nahmias V, Thermos K, Panagis G, Daifoti Z, Marselos M, Papahatjis D, Spyraki C. [2005] Behavioral pharmacological properties of a novel cannabinoid 1',1'-dithiolane delta8-THC analog, AMG-3. Behav Pharmacol. 16(5-6):499-510.

Malan et al[80] investigated the role of the CB2 cannabinoid receptor in regulation of peripheral pain, concluding "*These findings demonstrate the local, peripheral nature of CB(2) cannabinoid antinociception. .. Peripheral antinociception without CNS effects is consistent with the peripheral distribution of CB(2) receptors. CB(2) receptor agonists may have promise clinically for the treatment of pain without CNS cannabinoid side effects.*" Monhemius et al[81] noted the CB1 agonist WIN 55,212-2 "*markedly increased withdrawal latencies in the tail flick test and reduced responses to subcutaneous formalin. These effects were blocked by co-administration of (CB1 antagonist) SR141716A*" and concluded "*this system is important for the modulation of nociceptive transmission in an animal model of chronic neuropathic pain*" Similar results were reported by Drew et al[82], who concluded "*These results strengthen the body of evidence suggesting CB agonists may be an important novel analgesic approach for the treatment of sustained pain states.*" Nakamura et al[83] considered "*peripheral endogenous cannabinoids such as anandamide are novel candidates for mediators that inhibit the excitation of nociceptors*" Hanus et al[84] investigated the effects of a new CB2 receptor agonist (HU308), finding "*HU-308 reduces blood pressure, blocks defecation, and elicits anti-inflammatory and peripheral analgesic activity. The hypotension, the inhibition of defecation, the anti-inflammatory and peripheral analgesic effects produced by HU-308 are blocked (or partially blocked) by the CB(2) antagonist SR-144528, but not by the CB(1) antagonist SR-141716A. These results demonstrate the feasibility of discovering novel nonpsychotropic cannabinoids that may lead to new therapies for hypertension, inflammation, and pain.*"

Johanek & Simone[85] concluded "*cannabinoids primarily activate peripheral CB1 receptors to attenuate hyperalgesia. Activation of this receptor in the periphery may attenuate pain without causing unwanted side effects mediated by central CB1 receptors.*" McLaughlin et al[86] reported the CB1 receptor agonist "*AM 411 dose-dependently produced behaviors consistent with CB1 agonism, including analgesia... which were blocked by a CB1-selective antagonist.*" Maione et al[87] concluded "*endocannabinoids affect the descending pathways of pain control by acting at either CB(1) or TRPV1 receptors in healthy rats*" Elmes et al[88] concluded "*cannabinoid-based drugs have clinical potential for the treatment of established inflammatory pain responses*"

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80 Malan TP Jr, Ibrahim MM, Deng H, Liu Q, Mata HP, Vanderah T, Porreca F, Makriyannis A. [2001] CB2 cannabinoid receptor-mediated peripheral antinociception. Pain 93(3):239-45

81 Monhemius R, Azami J, Green DL, Roberts MH. [2001] CB1 receptor mediated analgesia from the Nucleus Reticularis Gigantocellularis pars alpha is activated in an animal model of neuropathic pain. Brain Res 908(1):67-74

82 Drew LJ, Harris J, Millns PJ, Kendall DA, Chapman V. [2000] Activation of spinal cannabinoid 1 receptors inhibits C-fibre driven hyperexcitable neuronal responses and increases [35S]GTPgammaS binding in the dorsal horn of the spinal cord of noninflamed and inflamed rats. Eur J Neurosci 12(6):2079-86

83 Nakamura A, Shiomi H. [1999] Recent advances in neuropharmacology of cutaneous nociceptors. Jpn J Pharmacol 79(4):427-31

84 Hanus L, Breuer A, Tchilibon S, Shiloah S, Goldenberg D, Horowitz M, Pertwee RG, Ross RA, Mechoulam R, Fride E. [1999] HU-308: a specific agonist for CB(2), a peripheral cannabinoid receptor. Proc Natl Acad Sci U S A 1999 Dec 7;96(25):14228-33

85 Johanek LM, Simone DA. [2004] Activation of peripheral cannabinoid receptors attenuates cutaneous hyperalgesia produced by a heat injury. Pain. (3):432-42.

86 McLaughlin PJ, Lu D, Winston KM, Thakur G, Swezey LA, Makriyannis A, Salamone JD. [2005] Behavioral effects of the novel cannabinoid full agonist AM 411. Pharmacol Biochem Behav. 81(1):78-88.

87 Maione S, Bisogno T, de Novellis V, Palazzo E, Cristino L, Valenti M, Petrosino S, Guglielmotti V, Rossi F, Marzo VD. [2006] Elevation of Endocannabinoid Levels in the Ventrolateral Periaqueductal Grey through Inhibition of Fatty Acid Amide Hydrolase Affects Descending Nociceptive Pathways via Both Cannabinoid Receptor Type 1 and Transient Receptor Potential Vanilloid Type-1 Receptors. J Pharmacol Exp Ther. 316(3):969-82.

88 Elmes SJ, Winyard LA, Medhurst SJ, Clayton NM, Wilson AW, Kendall DA, Chapman V. [2005] Activation of CB1 and CB2 receptors attenuates the induction and maintenance of inflammatory pain in the rat. Pain. 118(3):327-35.

An aerosol delivery system was tested in mice by Lichtman et al[89], who found "*The antinociceptive effects occurred within 5 min of exposure and lasted approximately 40 min in duration*" and noted "*inhalation exposure to Delta(9)-THC failed to produce two other indices indicative of cannabinoid activity, hypothermia and decreases in spontaneous locomotor activity*" Wiley et al[90] found the antinociceptive effects of different cannabinoids in rats depended upon the route of administration. Li et al[91] found "*low doses of cannabinoids, which do not produce analgesia or impair motor function, attenuate chemogenic pain and possess antihyperalgesic properties*" Valiveti et al[92] investigated permeation of cannabinoids across human skin with a view to developing products for topical application, and concluded "*The permeation results indicated that WIN 55,212-2 mesylate, CP 55,940, and other potent synthetic cannabinoids with these physicochemical properties could be ideal candidates for the development of a transdermal therapeutic system*."

Walker et al[93] concluded "*cannabinoids suppress nociceptive neurotransmission at the level of the spinal cord and the thalamus. These effects are reversible, receptor mediated, selective for painful as opposed to nonpainful somatic stimuli, and track the behavioral analgesia both in time course and potency*." Strangman et al[94] found "*cannabinoids inhibit the activity-dependent facilitation of spinal nociceptive responses*."

In monkeys, Manning et a found "*systemic administration of the prototypical opioid morphine or the cannabinoid receptor agonist WIN55,212-2 produced dose-dependent antinociception on a warm-water tail-withdrawal assay. The antinociceptive effects of each drug were reversible with an appropriate antagonist*" However the effect of the drug was significantly reduced in monkeys with amydaloid lesions, concluding "*the possibility should be considered that, in the primate, "antinociceptive circuitry" and "fear circuitry" overlap at the level of the amygdala*." Ko et al[95] found THC reduced responses to thermal and chemical pain in monkeys when applied locally.

In Amphibians, Salio et al[96] noted "*An endocannabinoid system is well developed... in the amphibian brain... cannabinoids might participate in the control of pain sensitivity also in the amphibian spinal cord*."

Interaction with opioid pain systems:

There is increasing evidence that the pain-relieving circuits modulated by endocannabinoids and opiates are closely-linked. Cichewicz & McCarthy[97] investigated synergy between THC and opiates in relieving pain, noting "*The*

89 Lichtman AH, Peart J, Poklis JL, Bridgen DT, Razdan RK, Wilson DM, Poklis A, Meng Y, Byron PR, Martin BR. [2000] Pharmacological evaluation of aerosolized cannabinoids in mice. Eur J Pharmacol 399(2-3):141-9

90 Wiley JL, Patrick GS, Crocker PC, Saha B, Razdan RK, Martin BR.[2000] Antinociceptive effects of tetrahydrocannabinol side chain analogs: dependence upon route of administration. Eur J Pharmacol 397(2-3):319-26

91 Li J, Daughters RS, Bullis C, Bengiamin R, Stucky MW, Brennan J, Simone DA [1999] The cannabinoid receptor agonist WIN 55,212-2 mesylate blocks the development of hyperalgesia produced by capsaicin in rats. Pain 81(1-2):25-33

92 Valiveti S, Kiptoo PK, Hammell DC, Stinchcomb AL. [2004] Transdermal permeation of WIN 55,212-2 and CP 55,940 in human skin in vitro. Int J Pharm. 278(1):173-80.

93 Walker JM, Hohmann AG, Martin WJ, Strangman NM, Huang SM, Tsou K. [1999] The neurobiology of cannabinoid analgesia. Life Sci 65(6-7):665-73

94 Strangman NM, Walker JM. [1999] Cannabinoid WIN 55,212-2 inhibits the activity-dependent facilitation of spinal nociceptive responses. J Neurophysiol 82(1):472-7

95 Ko MC, Woods JH. [1999] Local administration of delta9-tetrahydrocannabinol attenuates capsaicin-induced thermal nociception in rhesus monkeys: a peripheral cannabinoid action. Psychopharmacology (Berl) 143(3):322-6

96 Salio C, Cottone E, Conrath M, Franzoni MF. [2002] CB1 cannabinoid receptors in amphibian spinal cord: relationships with some nociception markers. J Chem Neuroanat. 24(3):153-62

97 Cichewicz DL, McCarthy EA. [2003] Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. J Pharmacol Exp Ther. 304(3):1010-5.

analgesic effects of opioids, such as morphine and codeine, in mice are enhanced by oral administration of the cannabinoid delta(9)-tetrahydrocannabinol (delta(9)-THC)."

Studying the interaction between cannabinoid and opioid systems in regulating pain & stress, Valverde et al[98] concluded "*CB1 receptors are not involved in the antinociceptive responses to exogenous opioids, but that a physiological interaction between the opioid and cannabinoid systems is necessary to allow the development of opioid-mediated responses to stress.*" Also, Mao et al[99] found "*The selective central cannabinoid receptor antagonist SR141716A, but not the generic opioid receptor antagonist naloxone, blocked the delta9-THC antinociception. Moreover, there is no cross-tolerance between the antinociceptive effects of morphine and delta9-THC in pathological pain states. ... the cannabinoid analgesic system may be superior to opioids in alleviating intractable pathological pain syndromes.*" Walkeret al[100] concluded "*The existence of a cannabinergic pain-modulatory system may have relevance for the treatment of pain, particularly in instances where opiates are ineffective.*" Salio et al[101] found "*A strong co-localization of CB1 and mu-opioid receptors was observed*"

Fuentes et al[102] concluded "*Current evidence indicate an interaction between cannabinoid and opioid systems, the latter being of known relevance in nociception. The fact that either exogenous or endogenous opioids enhanced cannabinoid-induced antinociception suggests simultaneous activation of both opioid and cannabinoid receptors by drugs as a new analgesic strategy."*

Yesilyurt et al[103] suggested a combination of topical and spinal cannabinoid/opiate therapy noting "*an antinociceptive interaction between topical opioids with topical, and spinal cannabinoids. These observations are significant in using of topical combination of cannabinoid and morphine in the management of pain.*" Dogrul et al[104] reported "*a reduction in the spinal CB1 receptors may enhance sensitivity to sensory stimuli and a decrease in spinal antinociceptive potency to cannabinoid agonists... 'knock-down' of spinal CB1 receptors apparently lowers the thresholds for sensory input*", Gardell et al[105] noted "*…antinociception produced by spinal cannabinoids are likely to be mediated directly through activation of cannabinoid receptors"* Yesilyurt & Dogrul[106] concluded "*opioids and cannabinoids produce antinociception through mechanisms that are independent of each other at either the systemic or peripheral levels.*" Vigano et al[107] commented "T*his might open up new therapeutic opportunities for relief of chronic pain through cannabinoid-opioid coadministration.*" Kim et al[108] suggested "*a direct action of anandamide on Na+ channels. The inhibition of Na+ currents in sensory neurons may*

98 Valverde O, Ledent C, Beslot F, Parmentier M, Roques BP. [2000] Reduction of stress-induced analgesia but not of exogenous opioid effects in mice lacking CB1 receptors. Eur J Neurosci 12(2):533-9

99 Mao J, Price DD, Lu J, Keniston L, Mayer DJ. [2000] Two distinctive antinociceptive systems in rats with pathological pain. Neurosci Lett 280(1):13-6

100 Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC [1999] Pain modulation by release of the endogenous cannabinoid anandamide. Proc Natl Acad Sci U S A 96(21):12198-203

101 Salio C, Fischer J, Franzoni MF, Mackie K, Kaneko T, Conrath M. [2001] CB1-cannabinoid and mu-opioid receptor co-localization on postsynaptic target in the rat dorsal horn. Neuroreport 12(17):3689-92

102 Fuentes JA, Ruiz-Gayo M, Manzanares J, Vela G, Reche I, Corchero J. [1999] Cannabinoids as potential new analgesics. Life Sci 65(6-7):675-85

103 Yesilyurt O, Dogrul A, Gul H, Seyrek M, Kusmez O, Ozkan Y, Yildiz O. [2003] Topical cannabinoid enhances topical morphine antinociception. Pain. 105(1-2):303-8.

104 Dogrul A, Gardell LR, Ma S, Ossipov MH, Porreca F, Lai J. [2002] 'Knock-down' of spinal CB1 receptors produces abnormal pain and elevates spinal dynorphin content in mice. Pain. 100(1-2):203-9.

105 Gardell LR, Ossipov MH, Vanderah TW, Lai J, Porreca F. [2002] Dynorphin-independent spinal cannabinoid antinociception. Pain. 100(3):243-8.

106 Yesilyurt O, Dogrul A. [2004] Lack of cross-tolerance to the antinociceptive effects of systemic and topical cannabinoids in morphine-tolerant mice. Neurosci Lett. 371(2-3):122-7.

107 Vigano D, Rubino T, Vaccani A, Bianchessi S, Marmorato P, Castiglioni C, Parolaro D. [2005] Molecular mechanisms involved in the asymmetric interaction between cannabinoid and opioid systems. Psychopharmacology (Berl). 182(4):527-36.

108 Kim HI, Kim TH, Shin YK, Lee CS, Park M, Song JH. [2005] Anandamide suppression of Na+ currents in rat dorsal root ganglion neurons. Brain Res. 1062(1-2):39-47.

contribute to the anandamide analgesia." Vaughan[109] concluded "*non-opioid SIA (stress-induced analgesia) is mediated by two independent endocannabinoids within the midbrain. Furthermore, novel agents that disrupt breakdown of these endocannabinoids enhance non-opioid SIA and pave the way for novel therapies*."

New Developments in cannabinoid receptor research

Development of synthetic cannabinoids are leading to an explosion of research into new applications[110]. Salio et al[111] noted the widespread distribution of CB-1 receptors and concluded "*ubiquitous localization may account for the complex role played by cannabinoids in antinociception*" Investigating the cannabinoid system in detail, Goutopolis et al[112] noted "*The four cannabinoid system proteins, including the CB(1) and CB(2) receptors, fatty acid amide hydrolase, and the anandamide transporter, are excellent targets for the development of novel medications for various conditions, including pain, immunosuppression, peripheral vascular disease, appetite enhancement or suppression, and motor disorders*." Wilson & Nicoll[113] noted "*In contrast to classical neurotransmitters, endogenous cannabinoids can function as retrograde synaptic messengers: They are released from postsynaptic neurons and travel backward across synapses, activating CB1 on presynaptic axons and suppressing neurotransmitter release. Cannabinoids may affect memory, cognition, and pain perception by means of this cellular mechanism*." Gardell et al[114] reported "*like opioids, repeated spinal administration of a cannabinoid CB1 agonist elicits abnormal pain, which results in increased expression of spinal dynorphin. Manipulations that block cannabinoid-induced pain also block the behavioral manifestation of cannabinoid tolerance*"

CB2-receptor studies: Malan et al[115] investigated the effect of CB-2 receptors on pain perception and observed "*CB(2) receptor activation is sufficient to inhibit acute nociception, inflammatory hyperalgesia, and the allodynia and hyperalgesia produced in a neuropathic pain model. Studies using site-specific administration of agonist and antagonist have suggested that CB(2) receptor agonists inhibit pain responses by acting at peripheral sites. CB(2) receptor activation also inhibits edema and plasma extravasation produced by inflammation. CB(2) receptor-selective agonists do not produce central nervous system (CNS) effects typical of cannabinoids*" They later concluded[116] "*CB(2) receptor activation inhibits acute, inflammatory and neuropathic pain responses in animal models. In preclinical studies, CB(2) receptor agonists do not produce central nervous system effects. Therefore, they show promise for the treatment of acute and chronic pain without psychoactive effects*." Ibrahim et al[117] found "*a mechanism leading to the inhibition of pain, one that targets receptors localized exclusively outside the CNS. Further, they suggest the potential use of CB2 receptor-selective agonists for treatment of human neuropathic pain, a condition currently without consistently effective therapies. CB2 receptor-selective agonist medications are predicted to be without the CNS side effects that limit the effectiveness of currently available medications*." Yoon & Choi[118] noted "*The antinociception of WIN 55,212-2 is*

109 Vaughan CW. [2006] Stressed-out endogenous cannabinoids relieve pain. Trends Pharmacol Sci. 27(2):69-71.
110 Pertwee RG [1999] Pharmacology of cannabinoid receptor ligands. Curr Med Chem 6(8):635-64
111 Salio C, Doly S, Fischer J, Franzoni MF, Conrath M. [2002] Neuronal and astrocytic localization of the cannabinoid receptor-1 in the dorsal horn of the rat spinal cord. Neurosci Lett. 329(1):13-6.
112 Goutopoulos A, Makriyannis A. [2002] From cannabis to cannabinergics: new therapeutic opportunities. Pharmacol Ther. 95(2):103-17.
113 Wilson RI, Nicoll RA. [2002] Endocannabinoid signaling in the brain. Science. 296(5568):678-82.
114 Gardell LR, Burgess SE, Dogrul A, Ossipov MH, Malan TP, Lai J, Porreca F [2002] Pronociceptive effects of spinal dynorphin promote cannabinoid-induced pain and antinociceptive tolerance. Pain. 98(1-2):79-88.
115 Malan TP Jr, Ibrahim MM, Vanderah TW, Makriyannis A, Porreca F. [2002] Inhibition of pain responses by activation of CB(2) cannabinoid receptors. Chem Phys Lipids. 121(1-2):191-200.
116 Malan TP Jr, Ibrahim MM, Lai J, Vanderah TW, Makriyannis A, Porreca F. [2003] CB2 cannabinoid receptor agonists: pain relief without psychoactive effects? Curr Opin Pharmacol. 3(1):62-7.
117 Ibrahim MM, Deng H, Zvonok A, Cockayne DA, Kwan J, Mata HP, Vanderah TW, Lai J, Porreca F, Makriyannis A, Malan TP Jr. [2003] Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS. Proc Natl Acad Sci U S A. 2003 100(18):10529-33.
118 Yoon MH, Choi JI. [2003] Pharmacologic interaction between cannabinoid and either clonidine or neostigmine in the rat formalin test. Anesthesiology. 99(3):701-7

mediated through the cannabinoid 1 receptor, but not the cannabinoid 2 receptor, at the spinal level." Dogrul et al[119] concluded "*there is an antinociceptive synergy between peripheral and spinal sites of cannabinoid action and it also implicates that local activation of cannabinoid system may regulate pain initiation in cutaneous tissue. Our findings support that cannabinoid system participates in buffering the emerging pain signals at the peripheral sites in addition to their spinal and supraspinal sites of action. In addition, an antinociceptive synergy between topical and spinal cannabinoid actions exists. These results also indicate that topically administered cannabinoid agonists may reduce pain without the dysphoric side effects and abuse potential of centrally acting cannabimimetic drugs*." Quartillo et al[120] concluded "*Local, peripheral CB2 receptor activation inhibits inflammation and inflammatory hyperalgesia. These results suggest that peripheral CB2 receptors may be an appropriate target for eliciting relief of inflammatory pain without the CNS effects of nonselective cannabinoid receptor agonists*." Hohmann et al[121] noted "*actions at cannabinoid CB(2) receptors are sufficient to normalize nociceptive thresholds and produce antinociception in persistent pain states*."

Scott et al[122] suggested "*a role for CB-2 receptor-mediated antinociception in both acute and neuropathic pain in addition to centrally located CB-1 mechanisms*." Nackley et al[123] noted "*activation of cannabinoid CB2 receptors is sufficient to suppress neuronal activity at central levels of processing in the spinal dorsal horn. Our findings are consistent with the ability of AM1241 to normalize nociceptive thresholds and produce antinociception in inflammatory pain states*." Ibrahim et al[124] concluded "*CB(2) receptor activation stimulates release from keratinocytes of beta-endorphin, which acts at local neuronal mu-opioid receptors to inhibit nociception... This mechanism allows for the local release of beta-endorphin, where CB(2) receptors are present, leading to anatomical specificity of opioid effects*." Valenzano et al[125] concluded "*CB2 receptor agonists have the potential to treat pain without eliciting the centrally-mediated side effects associated with non-selective cannabinoid agonists*" Sagar et al[126] observed "*At the level of the spinal cord, CB2 receptors have inhibitory effects in neuropathic, but not sham-operated rats suggesting that spinal CB2 may be an important analgesic target*". Fox & Bevan[127] advised "*The design of novel compounds that either specifically target peripheral CB(1) receptors or display high selectivity for CB(2) receptors may offer avenues for harnessing the analgesic effect of CB receptor agonists while avoiding the central adverse events seen with cannabinoid structures*." Wotherspoon et al[128] noted "*This clear demonstration of CB(2) receptors on sensory neurons suggests an additional cellular target for CB(2) agonist*

119 Dogrul A, Gul H, Akar A, Yildiz O, Bilgin F, Guzeldemir E. [2003] Topical cannabinoid antinociception: synergy with spinal sites. Pain. 105(1-2):11-6.

120 Quartilho A, Mata HP, Ibrahim MM, Vanderah TW, Porreca F, Makriyannis A, Malan TP Jr. [2003] Inhibition of inflammatory hyperalgesia by activation of peripheral CB2 cannabinoid receptors. Anesthesiology. 99(4):955-60.

121 Hohmann AG, Farthing JN, Zvonok AM, Makriyannis A. [2004] Selective activation of cannabinoid CB2 receptors suppresses hyperalgesia evoked by intradermal capsaicin. J Pharmacol Exp Ther. 308(2):446-53.

122 Scott DA, Wright CE, Angus JA. [2004] Evidence that CB-1 and CB-2 cannabinoid receptors mediate antinociception in neuropathic pain in the rat. Pain. 109(1-2):124-31.

123 Nackley AG, Zvonok AM, Makriyannis A, Hohmann AG. [2004] Activation of cannabinoid CB2 receptors suppresses C-fiber responses and windup in spinal wide dynamic range neurons in the absence and presence of inflammation. J Neurophysiol. 92(6):3562-74.

124 Ibrahim MM, Porreca F, Lai J, Albrecht PJ, Rice FL, Khodorova A, Davar G, Makriyannis A, Vanderah TW, Mata HP, Malan TP Jr. [2005] CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. Proc Natl Acad Sci U S A. 102(8):3093-8.

125 Valenzano KJ, Tafesse L, Lee G, Harrison JE, Boulet JM, Gottshall SL, Mark L, Pearson MS, Miller W, Shan S, Rabadi L, Rotshteyn Y, Chaffer SM, Turchin PI, Elsemore DA, Toth M, Koetzner L, Whiteside GT. [2005] Pharmacological and pharmacokinetic characterization of the cannabinoid receptor 2 agonist, GW405833, utilizing rodent models of acute and chronic pain, anxiety, ataxia and catalepsy. Neuropharmacology. 48(5):658-72

126 Sagar DR, Kelly S, Millns PJ, O'Shaughnessey CT, Kendall DA, Chapman V. [2005] Inhibitory effects of CB1 and CB2 receptor agonists on responses of DRG neurons and dorsal horn neurons in neuropathic rats. Eur J Neurosci. 22(2):371-9

127 Fox A, Bevan S. [2005] Therapeutic potential of cannabinoid receptor agonists as analgesic agents. Expert Opin Investig Drugs. 14(6):695-703.

128 Wotherspoon G, Fox A, McIntyre P, Colley S, Bevan S, Winter J. [2005] Peripheral nerve injury induces cannabinoid receptor 2 protein expression in rat sensory neurons. Neuroscience. 135(1):235-45.

induced analgesia, at least in neuropathic models." Whiteside et al[129], investigating the CB2-receptor agonist GW405833 in rats, concluded "*antihyperalgesic effects of GW405833 are mediated via the cannabinoid CB2 receptor, whereas the analgesic and sedative effects are not*", Labuda et al[130] concluded "*selective cannabinoid CB2 receptor agonists might represent a new class of postoperative analgesics*"

Clayton et al[131] found "*The CB2 agonist, 1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-(2-(morpholin-4-yl)ethyl)-1H-indole (GW405833) inhibited the hypersensitivity and was anti-inflammatory in vivo. These effects were blocked by SR144528. These findings suggest that CB1 receptors are involved in nociceptive pain and that both CB1 and CB2 receptors are involved in inflammatory hypersensitivity*." Elmes et al[132] concluded "*activation of peripheral CB2 receptors attenuates both innocuous- and noxious-evoked responses of WDR neurons in models of acute, inflammatory and neuropathic pain.*" Dajani et al[133] reported on CT3, a novel cannabinoid developed by Atlantic pharmaceuticals, noting "*CT-3 showed more prolonged duration of analgesic action than morphine (and)... warrants clinical development as a novel anti-inflammatory and analgesic drug*." Mason et al[134] postluated a "*critical role for dynorphin A release in the initiation of the antinociceptive effects of the cannabinoids at the spinal level*"

Palmitoylethanolamine (PEA) - Lambert et al[135] found palmitoyl-ethanolamine (PEA), a shorter and fully saturated analogue of anandamide to be "*found in most mammalian tissues... accumulated during inflammation and has been demonstrated to have a number of anti-inflammatory effects, including beneficial effects in clinically relevant animal models of inflammatory pain*" Di Marzo et al[136] considered cannabimimetic fatty acids to play a role in the control of tissue inflammation. In a 2002 review, Brune[137] concluded "*molecular biology and genomics have led to the development of new target-selective chemical entities for use in pain relief. These include .... blockers or agonists of cannabinoid and vanilloid receptors*"

Vanilloid/Capsiacin receptors - Studying capsiacin and vanilloid receptor responses to cannabinoids, Zygmunt et al[138] noted "*The THC response depends on extracellular calcium but does not involve known voltage-operated calcium channels, glutamate receptors, or protein kinases A and C. These results may indicate the presence of a novel cannabinoid receptor/ion channel in the pain pathway*." A similar study by Rukwied et al[139] described "*analgesic and anti-hyperalgesic properties of a topically applied cannabinoid*

129 Whiteside GT, Gottshall SL, Boulet JM, Chaffer SM, Harrison JE, Pearson MS, Turchin PI, Mark L, Garrison AE, Valenzano KJ. [2005] A role for cannabinoid receptors, but not endogenous opioids, in the antinociceptive activity of the CB2-selective agonist, GW405833. Eur J Pharmacol. 528(1-3):65-72.

130 LaBuda CJ, Koblish M, Little PJ. [2005] Cannabinoid CB2 receptor agonist activity in the hindpaw incision model of postoperative pain. Eur J Pharmacol. 527(1-3):172-4.

131 Clayton N, Marshall FH, Bountra C, O'Shaughnessy CT. [2002] CB1 and CB2 cannabinoid receptors are implicated in inflammatory pain. Pain. (3):253-60.

132 Elmes SJ, Jhaveri MD, Smart D, Kendall DA, Chapman V. [2004] Cannabinoid CB2 receptor activation inhibits mechanically evoked responses of wide dynamic range dorsal horn neurons in naive rats and in rat models of inflammatory and neuropathic pain. Eur J Neurosci. 20(9):2311-20.

133 Dajani EZ, Larsen KR, Taylor J, Dajani NE, Shahwan TG, Neeleman SD, Taylor MS, Dayton MT, Mir GN [1999] 1',1'-Dimethylheptyl-delta-8-tetrahydrocannabinol-11-oic acid: a novel, orally effective cannabinoid with analgesic and anti-inflammatory properties.. J Pharmacol Exp Ther 291(1):31-8

134 Mason DJ Jr, Lowe J, Welch SP. [1999] Cannabinoid modulation of dynorphin A: correlation to cannabinoid-induced antinociception. Eur J Pharmacol 378(3):237-48

135 Lambert DM, Vandevoorde S, Jonsson KO, Fowler CJ. (2002) The palmitoylethanolamide family: a new class of anti-inflammatory agents? Curr Med Chem 9(6):663-74

136 Di Marzo V, Melck D, De Petrocellis L, Bisogno T. [2000] Cannabimimetic fatty acid derivatives in cancer and inflammation. Prostaglandins Other Lipid Mediat 61(1-2):43-61

137 Brune K. [2002] Next generation of everyday analgesics. Am J Ther 9(3):215-23

138 Zygmunt PM, Andersson DA, Hogestatt ED. [2002] Delta 9-tetrahydrocannabinol and cannabinol activate capsaicin-sensitive sensory nerves via a CB1 and CB2 cannabinoid receptor-independent mechanism. J Neurosci. 22(11):4720-7.

139 Rukwied R, Watkinson A, McGlone F, Dvorak M. [2003] Cannabinoid agonists attenuate capsaicin-induced responses in human skin. Pain. 102(3):283-8.

receptor ligand, which might have important therapeutic implications in humans" Oshita et al[140] concluded "*CB(1)-receptor stimulation modulates the activities of transient receptor potential vanilloid receptor 1 in cultured rat DRG cells*." Singh Tahim et al[141] concluded "*inflammatory mediators significantly increase the excitatory potency and efficacy of anandamide on vanilloid type 1 transient receptor potential receptor, thus, increasing the anandamide concentration in, or around the peripheral terminals of nociceptors might rather evoke than decrease inflammatory heat hyperalgesia*." Szallasi[142] found "*arvanil, a combined agonist of VR1 and CB1 receptors, has already proved to be a powerful analgesic drug in the mouse*." Brooks et al[143] reported "*Activation of cannabinoid receptors causes inhibition of spasticity, in a mouse model of multiple sclerosis, and of persistent pain, in the rat formalin test. The endocannabinoid anandamide inhibits spasticity and persistent pain*", finding that anandamide is a full agonist of vanilloid receptors[144] which are associated with antispastic and analgesic activity.

Enzyme Studies: Cravatt & Lichtmann[145] investigated the possibility of blocking enzymes which break down anandamide to boost endocannabinoid activity, and noted "*anandamide, a natural lipid ligand for CB1, and an enzyme, fatty acid amide hydrolase (FAAH), that terminates anandamide signaling have inspired pharmacological strategies to augment endogenous cannabinoid ('endocannabinoid') activity with FAAH inhibitors*" Lichtmann et al[146] concluded "*selective inhibitors of FAAH might represent a viable pharmacological approach for the clinical treatment of pain disorders*", and later[147] reported FAAH inhibitors to "*raise central nervous system levels of anandamide and promote cannabinoid receptor 1-dependent analgesia in several assays of pain sensation.*" Rodella et al[148] considered the anadamide reuptake inhibitor "*AM404 could be a useful drug to reduce neuropathic pain and that cannabinoid CB1 receptor, cannabinoid CB2 receptor and vanilloid TRPV-1 receptor are involved*." Suplita et al[149] found "*In all conditions, the antinociceptive effects of each FAAH inhibitor were completely blocked by coadministration of the CB(1) antagonist rimonabant. The present results provide evidence that a descending cannabinergic neural system is activated by environmental stressors to modulate pain sensitivity in a CB(1)-dependent manner*."

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140 Oshita K, Inoue A, Tang HB, Nakata Y, Kawamoto M, Yuge O. [2005] CB(1) cannabinoid receptor stimulation modulates transient receptor potential vanilloid receptor 1 activities in calcium influx and substance P Release in cultured rat dorsal root ganglion cells. J Pharmacol Sci. 97(3):377-85.

141 Singh Tahim A, Santha P, Nagy I. [2005] Inflammatory mediators convert anandamide into a potent activator of the vanilloid type 1 transient receptor potential receptor in nociceptive primary sensory neurons. Neuroscience. 136(2):539-48.

142 Szallasi A [2001] Vanilloid receptor ligands: hopes and realities for the future. Drugs Aging 18(8):561-73

143 Brooks JW, Pryce G, Bisogno T, Jaggar SI, Hankey DJ, Brown P, Bridges D, Ledent C, Bifulco M, Rice AS, Di Marzo V, Baker D [2002] Arvanil-induced inhibition of spasticity and persistent pain: evidence for therapeutic sites of action different from the vanilloid VR1 receptor and cannabinoid CB(1)/CB(2) receptors. Eur J Pharmacol 439(1-3):83-92

144 Di Marzo V, Griffin G, De Petrocellis L, Brandi I, Bisogno T, Williams W, Grier MC, Kulasegram S, Mahadevan A, Razdan RK, Martin BR. [2002] A structure/activity relationship study on arvanil, an endocannabinoid and vanilloid hybrid. J Pharmacol Exp Ther 300(3):984-91

145 Cravatt BF, Lichtman AH. [2003] Fatty acid amide hydrolase: an emerging therapeutic target in the endocannabinoid system. Curr Opin Chem Biol. 7(4):469-75

146 Lichtman AH, Shelton CC, Advani T, Cravatt BF. [2004] Mice lacking fatty acid amide hydrolase exhibit a cannabinoid receptor-mediated phenotypic hypoalgesia. Pain. 109(3):319-27

147 Lichtman AH, Leung D, Shelton CC, Saghatelian A, Hardouin C, Boger DL, Cravatt BF. [2004] Reversible inhibitors of fatty acid amide hydrolase that promote analgesia: evidence for an unprecedented combination of potency and selectivity. J Pharmacol Exp Ther. 311(2):441-8.

148 Rodella LF, Borsani E, Rezzani R, Ricci F, Buffoli B, Bianchi R. [2005] AM404, an inhibitor of anandamide reuptake decreases Fos-immunoreactivity in the spinal cord of neuropathic rats after non-noxious stimulation. Eur J Pharmacol. 508(1-3):139-46.

149 Suplita RL 2nd, Farthing JN, Gutierrez T, Hohmann AG. [2005] Inhibition of fatty-acid amide hydrolase enhances cannabinoid stress-induced analgesia: sites of action in the dorsolateral periaqueductal gray and rostral ventromedial medulla. Neuropharmacology. 49(8):1201-9.

Jayamane et al[150] concluded "*FAAH inhibitor URB597 produces cannabinoid CB(1) and CB(2) receptor-mediated analgesia in inflammatory pain states, without causing the undesirable side effects associated with cannabinoid receptor activation*" La Rana et al[151] found "*a role of the endocannabinoid system in pain modulation and point to anandamide transport as a potential target for analgesic drug development*" De Lago[152] et al studied the effects of UCM707, an endocannabinoid reuptake inhibitor, and commented "*UCM707, as suggested by its in vitro properties, seems also to behave in vivo as a selective and potent inhibitor of the endocannabinoid transporter, showing negligible direct effects on the receptors for endocannabinoids but potentiating the action of these endogenous compounds*."

Human Studies & Clinical Trials

Although Whiteley[153] noted "*human studies are few and far between and have been held up by the law and the lack of standardised extracts*", in recent years, many clinical trials have been performed on cannabis-based medicines and individual cannabinoids.

In early studies, Mechoulam found inconclusive results on pain relief from human subjects, although the dosages in most studies were lower than those found effective in animal models. He concluded that there was "*significant analgesic activity*" from THC, remarking that the lack of any physical dependence was "a plus", although he was concerned about the "*psychotomimetic*" effects (i.e. the high) particularly for individuals unused to the drug. In an earlier review[154] Mechoulam had considered the traditional use of cannabis preparations as analgesic and anti-rheumatic agents to have "some modern substantiation".

Noyes et al[155] found a clear dose-related analgesic effect from oral administration of THC. In a second study[156] the analgesic effect was found to be six times as powerful as that of codeine, with 20mg THC producing significant pain relief for over 5 hours. He considered the side effects (sedation and light-headedness) to mitigate against wider clinical use. However, his subjects were inexperienced with marijuana use and as such may have found the psychological effects of the high more disturbing, and thus less tolerable, than experienced users. Milstein et al[157] found that experienced marijuana users exposed to approximately 7.5mg THC by inhalation, achieved a greater analgesic effect than naive subjects, and were less likely to report adverse side effects. Whether this increased response is due to more efficient inhalation techniques in the experienced group, or through a "reverse tolerance" whereby THC has a greater effect in habitués, is not clear.

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150 Jayamanne A, Greenwood R, Mitchell VA, Aslan S, Piomelli D, Vaughan CW. [2006] Actions of the FAAH inhibitor URB597 in neuropathic and inflammatory chronic pain models. Br J Pharmacol. 147(3):281-8.

151 La Rana G, Russo R, Campolongo P, Bortolato M, Mangieri RA, Cuomo V, Iacono A, Mattace Raso G, Meli R, Piomelli D, Calignano A. [2006] Modulation of neuropathic and inflammatory pain by the endocannabinoid transport inhibitor AM404. J Pharmacol Exp Ther. Mar 1; [Epub ahead of print]

152 de Lago E, Fernandez-Ruiz J, Ortega-Gutierrez S, Viso A, Lopez-Rodriguez ML, Ramos JA. [2002] UCM707, a potent and selective inhibitor of endocannabinoid uptake, potentiates hypokinetic and antinociceptive effects of anandamide. Eur J Pharmacol. 449(1-2):99-103.

153 Whiteley NJ. [2002] Do cannabinoid drugs have a therapeutic value as analgesics? Prof Nurse. 18(1):51-3

154 Mechoulam R. (1980) Current Status of Therapeutic Opportunities based on Cannabinoid Research - An Overview. Journal of Clinical Pharmacology 21 pp2-7

155 Noyes R, Brunk SF, Baram DA & Canter A [1975] Analgesic effect of Delta-9-tetrahydrocannabinol. Journal of Clinical Pharmacology 15 (2,3) pp139-143

156 Noyes R, Brunk SF, Avery DH & Canter A [1975] The analgesic properties of Delta-9-tetrahydrocannabinol and codeine. Clinical Pharmacology & Therapeutics 18 (1) pp84-89

157 Milstein SL, MacCannell K, Karr G & Clark S [1975] Marijuana-produced changes in pain tolerance - experienced and non-experienced subjects. International Pharmacopsychiatry 10 pp177-182

Pertwee[158] reports a number of patients suffering spinal injury or multiple sclerosis claiming cannabis relieves spasticity and pain associated with muscle spasms more effectively than conventional muscle relaxants and with more tolerable side effects. Several clinical trials have supported these claims[159 160 161], indicating that oral THC or inhalation of cannabis smoke can relieve muscle pain and spasticity. In a small-scale clinical trial of THC, Elsner et al[162] found half the patients achieved sufficient pain relief, but noted "*large individual differences in the effectiveness of THC in pain management*"

Burstein[163] finds evidence that the carboxylic acid derivatives of THC and other cannabinoids may have potent analgesic and/or anti-inflammatory activity. Several of these derivatives are present in the body fluids of cannabis users as non-psychoactive metabolites of the drug. These derivatives may offer a potential advantage in that they are more water-soluble than THC. Jbilo et al[164], studing the effects of gene expression on human cannabinoid receptors, reported: '*our data highlight a possible new function of peripheral cannabinoid receptors in the modulation of immune and inflammatory responses* '

Williamson & Evans[165] noted "*Small clinical studies have confirmed the usefulness of THC as an analgesic; CBD and CBG also have analgesic and antiinflammatory effects*" Vaughan & Christie[166] concluded "*Cannabinoids have significant analgesic properties in animal models, particularly for chronic pain states, but there are few human studies. Well-controlled clinical trials on cannabinoids, and cannabinoid delivery systems, are now required.*" Kinzbrunner[167] criticised the "*adverse psychotropic effects*" of cannabis but conceded "*cannabinoids and codeine have similar effects on pain relief*" Elsner et al[168] reviewed 6 pain patients treated with THC (oral, 5-20mg/d) finding large individual differences in the analgesic response, 3 patients achieving satisfactory pain relief, the other three experiencing "*intolerable side effects such as nausea, dizziness and sedation without a reduction of pain intensity*"

Haney et al[169] studying responses of 12 subjects to active and placebo marijuana cigarettes, postulated a cannabis withdrawal syndrome, reporting "*Abstinence from active marijuana increased ratings such as "Anxious," "Irritable," and "Stomach pain,"*

158 Pertwee RG (1995) Pharmacological, physiological and other clinical implications for the discovery of cannabinoid receptors: an overview. In Pertwee RG (Ed) Cannabis Receptors. London: Academic Press. pp1-34

159 Petro DJ & Ellenberger C. (1981) Treatment of human spasticity with D9 tetrahydrocannabinol. J Clin Pharmacol. (Suppl) 21 pp413s-416s.

160 Meinck H-M et al (1989) Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. J. Neurol 236 pp120-122

161 Maurer M et al (1990) Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. Eur Arch Psychiatry Clin Neurosci. 240 pp1-4

162 Elsner F, Radbruch L, Sabatowski R. [2001] Tetrahydrocannabinol zur Therapie chronischer Schmerzen Tetrahydrocannabinol for treatment of chronic pain. Schmerz 15(3):200-4

163 Burstein SH (1999) The cannabinoid acids: nonpsychoactive derivatives with therapeutic potential. Pharmacol Ther 82(1):87-96

164 Jbilo O, Derocq JM, Segui M, Le Fur G, Casellas P (1999) Stimulation of peripheral cannabinoid receptor CB2 induces MCP-1 and IL-8 gene expression in human promyelocytic cell line HL60. FEBS Lett 448(2-3):273-7

165 Williamson EM, Evans FJ. [2000] Cannabinoids in clinical practice. Drugs 60(6):1303-14

166 Vaughan CW, Christie MJ. [2000] An analgesic role for cannabinoids Med J Aust 173(5):270-2

167 Kinzbrunner BM. [2002] Review: cannabinoids and codeine have similar effects on pain relief, but cannabinoids commonly cause adverse psychotropic effects. ACP J Club 136(1):18 (Comment on: BMJ. 2001 Jul 7;323(7303):13-6.)

168 Elsner F, Radbruch L, Sabatowski R.Schmerz [2001] Tetrahydrocannabinol zur Therapie chronischer Schmerzen Tetrahydrocannabinol for treatment of chronic pain. Jun;15(3):200-4

169 Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. [1999] Abstinence symptoms following smoked marijuana in humans. Psychopharmacology (Berl) 141(4):395-404

and significantly decreased food intake compared to baseline." Haney et al[170] administered the opioid antagonist naltrexone to marijuana smokers, and reported "*naltrexone increases the subjective effects of oral THC. Thus, oral THC's effects are enhanced rather than antagonized by opioid receptor blockade in heavy marijuana smokers*."

Clermont-Gnamien et al[171] treated chronic pain patients with oral THC and noted "*THC did not induce significant effect on the various pain, HRQL and anxiety and depression scores. Numerous side effects (notably sedation and asthenia) were observed in 5 patients out of 7, requiring premature discontinuation of the drug in 3 patients... The present study did not reveal any significant efficacy of THC in a small cohort of patients with chronic refractory neuropathic pain, but underlined the unfavorable side effect profile of the drug. These results may partly relate to the fact that oral dronabinol exhibits a poor therapeutic ratio (efficacy at the price of side effects)*." In Denmark, a trial of Dronabinol among MS patients by Svendsen et al[172] found "*Dronabinol reduced the spontaneous pain intensity significantly compared with placebo (4.0 (2.3-6.0) vs. 5.0 (4.0-6.4), median (25th-75th percentiles), p = 0.02). Though dronabinol's analgesic effect is modest, its use should be evaluated considering the general difficulty in treating central pain*"

Naef et al[173] tested THC, Morphine and a combination on induced pain in healthy volunteers, and reported "*THC did not significantly reduce pain. In the cold and heat tests it even produced hyperalgesia, which was completely neutralized by THC-morphine. A slight additive analgesic effect could be observed for THC-morphine in the electrical stimulation test. No analgesic effect resulted in the pressure and heat test, neither with THC nor THC-morphine. Psychotropic and somatic side-effects (sleepiness, euphoria, anxiety, confusion, nausea, dizziness, etc.) were common, but usually mild.*" Roberts et al[174] found "*neither morphine nor Delta(9)-THC had a significant effect, there was a positive analgesic interaction between the two (p = 0.012), indicating that the combination had a synergistic affective analgesic effect*" however Seeling et al[175] found "*neither a synergistic nor even an additive antinociceptive interaction between (9)-tetrahydrocannabinol and the mu-opioid agonist piritramide in a setting of acute postoperative pain.*"

Killestein et al[176] conducted a clinical trial of oral THC and cannabis plant extracts on 16 MS patients, and noted "*Both drugs were safe, but adverse events were more common with plant-extract treatment. Compared with placebo, neither THC nor plant-extract treatment reduced spasticity.*" Following a clinical trial of cannabis plant extracts, Wade et al[177] reported "*Pain relief associated with both THC and CBD was significantly superior to placebo... Cannabis medicinal extracts can improve neurogenic symptoms unresponsive to standard treatments. Unwanted effects are predictable and*

170 Haney M, Bisaga A, Foltin RW. [2003] Interaction between naltrexone and oral THC in heavy marijuana smokers. Psychopharmacology (Berl). 166(1):77-85.

171 Clermont-Gnamien S, Atlani S, Attal N, Le Mercier F, Guirimand F, Brasseur L. [2002] [The therapeutic use of D9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain] [Article in French] Presse Med. 31(39 Pt 1):1840-5.

172 Svendsen KB, Jensen TS, Bach FW. [2005] [Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis--secondary publication] [Article in Danish] Ugeskr Laeger. 167(25-31):2772-4.

173 Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. [2003] The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain. 105(1-2):79-88.

174 Roberts JD, Gennings C, Shih M. [2006] Synergistic affective analgesic interaction between delta-9-tetrahydrocannabinol and morphine. Eur J Pharmacol. 530(1-2):54-8.

175 Seeling W, Kneer L, Buchele B, Gschwend JE, Maier L, Nett C, Simmet T, Steffen P, Schneider M, Rockemann M. [2006] [(9)-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain.] [Article in German] Anaesthesist. [3-1-06 Epub ahead of print]

176 Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG, Gorter RW, Uitdehaag BM, Polman CH. [2002] Safety, tolerability, and efficacy of orally administered cannabinoids in MS. Neurology. 58(9):1404-7.

177 Wade DT, Robson P, House H, Makela P, Aram J. [2003] A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 17(1):21-9.

generally well tolerated." Berman et al[178] reported "*The (mean pain severity score) failed to fall by the two points defined in our hypothesis. However, both this measure and measures of sleep showed statistically significant improvements. The study medications were generally well tolerated with the majority of adverse events, including intoxication type reactions, being mild to moderate in severity and resolving spontaneously"* In a trial on trigeminal neuralgia Liang et al[179] concluded "*cannabinoids may prove useful in pain modulation by inhibiting neuronal transmission in pain pathways. Considering the pronounced antinociceptive effects produced by cannabinoids, they may be a promising therapeutic approach for the clinical management of trigeminal neuralgia*"

A clinical trial of oral THC by Buggy et al[180] found "*no evidence of an analgesic effect of orally administered delta-9-THC 5 mg in postoperative pain in humans*.", a similar trial by Attal et al[181] found "*THC (mean dosage: 16.6+/-6.5 mg/day) did not induce any significant effects on ongoing and paroxysmal pain, allodynia, quality of life, anxiety/depression scores and functional impact of pain. These results do not support an overall benefit of THC in pain and quality of life in patients with refractory neuropathic pain*" In a trial of Dronabinol on MS patients, Svendsen et al[182] concluded "*Dronabinol has a modest but clinically relevant analgesic effect on central pain in patients with multiple sclerosis. Adverse events, including dizziness, were more frequent with dronabinol than with placebo during the first week of treatment*."

After a clinical trial of 1',1'dimethylheptyl-Delta8-tetrahydrocannabinol-11-oic acid (CT-3), a potent analogue of THC-11-oic acid, Karst et al[183] concluded "*CT-3 was effective in reducing chronic neuropathic pain compared with placebo. No major adverse effects were observed*" In a separate trial of CT3, Burstein et al[184] found "*In preclinical studies (CT3) displayed many of the properties of non-steroidal anti-inflammatory drugs (NSAIDs); however, it seems to be free of undesirable side effects. The initial short-term trials in healthy human subjects, as well as in patients with chronic neuropathic pain, demonstrated a complete absence of psychotropic actions. Moreover, it proved to be more effective than placebo in reducing this type of pain as measured by the visual analog scale. Unlike the narcotic analgesics, signs of dependency were not observed after withdrawal of the drug at the end of the one-week treatment period*." Salim et al[185] found ajulemic acid (CT3) "*shows pain-reducing effects on patients with chronic neuropathic pain without clinically relevant psychotropic or physical side effects*"

A study of nabilone in 20 chronic pain patients by Berlach et al[186] found "*Fifteen patients reported subjective overall improvement with nabilone, and nine reported reduced pain intensity. Beneficial effects on sleep and nausea were the main reasons for continuing use. Intolerable side effects were experienced in three patients (palpitations, urinary retention, dry mouth). Nabilone may be a useful addition to pain management and should be further evaluated in randomized controlled trials*."

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178 Berman JS, Symonds C, Birch R. [2004] Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 112(3):299-306.

179 Liang YC, Huang CC, Hsu KS. [2004] Therapeutic potential of cannabinoids in trigeminal neuralgia. Curr Drug Targets CNS Neurol Disord. 3(6):507-14.

180 Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ. [2003] Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. Pain. 106(1-2):169-72

181 Attal N, Brasseur L, Guirimand D, Clermond-Gnamien S, Atlami S, Bouhassira D. [2004] Are oral cannabinoids safe and effective in refractory neuropathic pain? Eur J Pain. 8(2):173-7.

182 Svendsen KB, Jensen TS, Bach FW. [2004] Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 329(7460):253.

183 Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. [2003] Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. 290(13):1757-62.

184 Burstein SH, Karst M, Schneider U, Zurier RB. [2004] Ajulemic acid: A novel cannabinoid produces analgesia without a "high". Life Sci. 75(12):1513-22.

185 Salim K, Schneider U, Burstein S, Hoy L, Karst M. [2005] Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. Neuropharmacology. 48(8):1164-71.

186 Berlach DM, Shir Y, Ware MA. [2006] Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. Pain Med. 7(1):25-9.

Sativex Trials - In 2003 GW Pharmaceuticals[187] announced ongoing clinical trials of cannabis extracts (Sativex) for the following conditions:

(a) *the relief of pain of neurological origin and defects of neurological function in the following indications: multiple sclerosis (MS), spinal cord injury, peripheral nerve injury, central nervous system damage, neuroinvasive cancer, dystonias, cerebral vascular accident and spina bifida, as well as for the relief of pain and inflammation in rheumatoid arthritis and also pain relief in brachial plexus injury.*

(b) *spasticity and bladder dysfunction in multiple sclerosis patients*

(c) *spinal cord injury*

(d) *High CBD in various CNS disorders (including epilepsy, stroke and head injury).*

(e) *THC:CBD (broad ratio) in patients with inflammatory bowel disease*

(f) *High CBD in patients with psychotic disorders such as schizophrenia, and a preclinical trial of High CBD in various CNS disorders (including epilepsy, stroke and head injury).*

(g) *THC:CBD (narrow ratio) in the following medical conditions: pain in spinal cord injury, pain and sleep in MS and spinal cord injury, neuropathic pain in MS and general neuropathic pain (presented as allodynia). Results from these trials show that THC:CBD (narrow ratio) caused statistically significant reductions in neuropathic pain in patients with MS and other conditions. In addition, improvements in other MS symptoms were observed as well.*

(h) *THC:CBD (broad ratio) in a small number of patients with rheumatoid arthritis.*

In September 2001, preliminary results were reported from the GW Pharmaceuticals clinical trials of a sub-lingual cannabis-extract spray on pain management: "*Only one of the 23 patients failed to benefit from the cannabis spray and two others dropped out because of side effects. The remaining 18 experienced pain relief that varied from moderate ("at least I can sleep at night") to dramatic ("it has transformed my life"). Patients on morphine to control severe pain were able to cut their doses dramatically.*"[188]

In November 2002 the results of phase III trials were announced by GW Pharmaceuticals[189] "*In a double-blind crossover study comparing the efficacy of GW's THC:CBD product, GW's THC alone product and placebo in the treatment of neuropathic pain in 48 patients with Brachial Plexus Injury, both the THC:CBD medicine and the THC medicine provided highly statistically significant relief of pain and statistically significant reduction in sleep disturbance. Brachial plexus injury is a rare but particularly challenging cause of intractable neuropathic pain, and to the best of our knowledge this is the first placebo-controlled trial ever conducted in this condition. The benefits seen in all four studies are all the more notable in that they represent improvements over and above that which patients obtain with their standard prescription medicines (patients receiving both active and placebo medicines continued to take their standard prescription medicines during the trial).*"

In a UK clinical trial of cannabis extracts on MS symptoms, Zajicek et al found "*objective improvement in mobility and patients' opinion of an improvement in pain (which) suggest cannabinoids might be clinically useful*" In a sister trial of chronic pain Notcutt et al[190] noted "*Extracts which contained THC proved most effective in symptom control. Regimens for the use of the sublingual spray emerged and a wide range of dosing requirements was observed. Side-effects were common, reflecting a learning curve for both patient and study team. These were generally acceptable and little different to those seen when other psycho-active agents are used for chronic pain.*" An open-label trial on MS patients by Brady et al[191] found "*Patient self-assessment of pain, spasticity and quality of sleep improved significantly (P <0.05, Wilcoxon's signed rank test) with pain improvement*

187 [No authors listed] [2003] Cannabis-based medicines--GW pharmaceuticals: high CBD, high THC, medicinal cannabis--GW pharmaceuticals, THC:CBD. Drugs R D. 4(5):306-9.

188 Notcutt W & Williamson E (2001) British Association Science Festival, Glasgow. Reported in Cookson C - "High Hopes For Cannabis To Relieve Pain" Financial Times 4-9-01

189 http://www.gwpharm.com/news_pres_05_nov_02.html

190 Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C. [2004] Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia. 59(5):440-52.

191 Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. [2004] An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Mult Scler. 10(4):425-33.

continuing up to median of 35 weeks." Szendrei[192] commented on the potential of Sativex in European medicine "*The new analgesic is proposed for the treatment of muscle spasticity and pains accompanying multiple sclerosis and as an efficient analgetic for neurogenic pain not responding well to opioids and to other therapies available*."

Wade et al[193] investigated Sativex in MS patients, finding "*Following CBME the primary symptom score reduced from mean (SE) 74.36 (11.1) to 48.89 (22.0) following CBME and from 74.31 (12.5) to 54.79 (26.3) following placebo [ns]. Spasticity VAS scores were significantly reduced by CBME (Sativex) in comparison with placebo (P =0.001). There were no significant adverse effects on cognition or mood and intoxication was generally mild*." In a further UK trial of Sativex by Rog et al[194] found it "s*uperior to placebo in reducing the mean intensity of pain… and sleep disturbance*" concluding "*Cannabis-based medicine is effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain and is mostly well tolerated*." Blake et al[195] found "*In comparison with placebo, (sativex) produced statistically significant improvements in pain on movement, pain at rest, quality of sleep*" Perras[196] reported "*In some trials, THC:CBD spray significantly reduced neuropathic pain, spasticity, muscle spasms and sleep disturbances. The most common adverse events (AEs) reported in trials were dizziness, sleepiness, fatigue, feeling of intoxication and a bad taste*."

Russo & Guy[197], reviewing the clinical trials of sativex, noted "*CBD is demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right. In modern clinical trials, this has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain… The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported*."

Learned Reviews & Therapeutic Assessments

Assessing the oral route of administration of cannabinoid medicines, Pertwee[198] concluded "*When taken orally, THC seems to undergo variable absorption and to have a narrow 'therapeutic window' (dose range in which it is effective without producing significant unwanted effects). This makes it difficult to predict an oral dose that will be both effective and tolerable to a patient and indicates a need for better cannabinoid formulations and modes of administration*" Pertwee summarised in a 2001 review "*Mammalian tissues contain at least two types of cannabinoid receptor, CB(1) and CB(2)... CB(1) receptors are expressed mainly by neurones of the central and peripheral nervous system whereas CB(2) receptors occur centrally and peripherally in certain non-neuronal tissues, particularly in immune cells... antinociception can be mediated by cannabinoid receptors other than CB(1) and CB(2) receptors, for example CB(2)-like receptors... one endogenous cannabinoid, anandamide, produces antinociception through mechanisms that differ from those of other*

192 Szendrei K. [2004] [A novel analgesics made from Cannabis] [Article in Hungarian] Ideggyogy Sz. 57(1-2):36-40.

193 Wade DT, Makela P, Robson P, House H, Bateman C. [2004] 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. 10(4):434-41. * Mult Scler. 2004 Aug;10(4):339-40.

194 Rog DJ, Nurmikko TJ, Friede T, Young CA. [2005] Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 65(6):812-9.

195 Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. [2006] 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). 45(1):50-2.

196 Perras C. [2005] Sativex for the management of multiple sclerosis symptoms. Issues Emerg Health Technol. (72):1-4.

197 Russo E, Guy GW. [2006] A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 66(2):234-46.

198 Pertwee RG. [1999] Cannabis and cannabinoids: pharmacology and rationale for clinical use. Forsch Komplementarmed 6 Suppl 3:12-5

types of cannabinoid, for example by acting on vanilloid receptor... the endocannabinoid system has physiological and/or pathophysiological roles in the modulation of pain."

In a 2001 review, Rice[199] noted "*Strong laboratory evidence now underwrites anecdotal claims of cannabinoid analgesia in inflammatory and neuropathic pain*." Tsou et al[200] concluded "*cannabinoids inhibit the spinal processing of nociceptive stimuli and ... endogenous cannabinoids may act naturally to modify pain transmission within the central nervous system*." Welch et al[201] reported "*Delta(9)-THC and morphine can be useful in low dose combination as an analgesic. .. We hypothesize the existence of a new CB receptor differentially linked to endogenous opioid systems ... Such a receptor, due to the release of endogenous opioids, may have significant impact upon the clinical development of cannabinoid/opioid combinations for the treatment of a variety of types of pain in humans*" Martin & Lichtman[202] concluded "*The use of cannabis for the management of a wide range of painful disorders has been well documented in case reports throughout history. ... THC and its synthetic derivatives have been shown to be effective in most animal models of pain. These antinociceptive effects are mediated through cannabinoid receptors in the brain that in turn appear to interact with noradrenergic and kappa opioid systems in the spinal cord to modulate the perception of painful stimuli. The endogenous ligand, anandamide, is also an effective antinociceptive agent*." When considering options for postoperative pain,Dahl & Raeder[203] concluded "*cannabinoids... may become important analgesic drugs*."

In a review article for the BMJ, Campbell et al[204] considered "*Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid randomised controlled studies are needed*." This sparked a lively debate in the letters pages with Campbell's review being widely-criticised. Curatolo et al[205], following a general review of pain management options, concluded "*Cannabinoid agents produce antinociception and prevent experimentally induced hyperalgesia in animals, and they may find a role in pain management*" Iversen[206] concluded "*cannabinoid agonists are antihyperalgesic and antiallodynic in models of neuropathic pain*", but also warned[207] "*Few well controlled trials of cannabis exist for systemic review."*

Du Pont[208], opposing the use of medical marijuana, warned "*most supporters of smoked marijuana are hostile to the use of purified chemicals from marijuana, insisting that only smoked marijuana leaves be used as "medicine," revealing clearly that their motivation is not scientific medicine but the back door legalization of marijuana*.". In response, Rosenthal

199 Rice AS. [2001] Cannabinoids and pain. Curr Opin Investig Drugs 2(3):399-414

200 Tsou K, Lowitz KA, Hohmann AG, Martin WJ, Hathaway CB, Bereiter DA, Walker JM. [1996] Suppression of noxious stimulus-evoked expression of Fos protein-like immunoreactivity in rat spinal cord by a selective cannabinoid agonist. Neuroscience 70(3):791-8

201 Welch SP, Eads M. Welch SP, Eads M. [1999] Synergistic interactions of endogenous opioids and cannabinoid systems. Brain Res 848(1-2):183-90

202 Martin BR, Lichtman AH (1998) Cannabinoid transmission and pain perception. Neurobiol Dis 5(6 Pt B):447-61

203 Dahl V, Raeder JC. [2000] Non-opioid postoperative analgesia. Acta Anaesthesiol Scand 44(10):1191-203

204 Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. [2001] Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ 323(7303):13

205 Curatolo M, Bogduk N. [2001] Pharmacologic pain treatment of musculoskeletal disorders: current perspectives and future prospects. Clin J Pain 17(1):25-32

206 Iversen L, Chapman V. [2002] Cannabinoids: a real prospect for pain relief? Curr Opin Pharmacol 2(1):50-5

207 Iversen L. [2001] Cannabinoids in pain management. Few well controlled trials of cannabis exist for systemic review. BMJ 323(7323):1250; discussion 1250-1 (Comment on: BMJ. 2001 Jul 7;323(7303):13-6.)

208 DuPont RL. [1999] Examining the debate on the use of medical marijuana. Proc Assoc Am Physicians 1999 Mar-Apr;111(2):166-72

& Kleber[209] proposed "*parallel trials on those indications under careful controls making marijuana available to appropriate patients who fail to benefit from standard existing treatments*."

Hollister[210] considered smoked marijuana should be investigated for efficacy in conditions including chronic pain syndrome. Clark[211] argued "*there is a proportionate reason for allowing physicians to prescribe marijuana. Seriously ill patients have the right to effective therapies. To deny patients access to such a therapy is to deny them dignity and respect as persons*." The US Institute of Medicine[212] concluded "*the available evidence from human and animal studies indicates that cannabinoids can have a substantial analgesic effect*."

In 2002 reviews, Pertwee & Ross[213] observed "*Potential therapeutic uses of cannabinoid receptor agonists include the management of multiple sclerosis/spinal cord injury, pain, inflammatory disorders, glaucoma, bronchial asthma, vasodilation that accompanies advanced cirrhosis, and cancer*." Pertwee[214] also noted "*There is a growing amount of evidence to suggest that cannabis and individual cannabinoids may be effective in suppressing certain symptoms of multiple sclerosis and spinal cord injury, including spasticity and pain... Future research should also be directed at obtaining more conclusive evidence about the efficacy of cannabis or individual cannabinoids against the signs and symptoms of these disorders, at devising better modes of administration for cannabinoids and at exploring strategies that maximize separation between the sought-after therapeutic effects and the unwanted effects of these drugs*." Fride[215] noted "*Endocannabinoids have been implicated in a variety of physiological functions. The areas of central activities include pain reduction, motor regulation, learning/memory, and reward*." Walker & Huang[216] reported "*endocannabinods function to control pain in parallel with endogenous opioids but via different mechanisms*" adding[217] "*Multiple lines of evidence indicate that endocannabinoids serve naturally to suppress pain. While it is now clear that cannabinoids suppress nociceptive neurotransmission, more work is needed to establish the clinical utility of these compounds. The few human studies conducted to date produced mixed results, with more promising findings coming from studies of clinical pain as compared with experimental pain*." Rice et al[218] stated "*Whilst a proportion of the peripheral analgesic effect of endocannabinoids can be attributed to a neuronal mechanism acting through CB(1) receptors expressed by primary afferent neurones, the antiinflammatory actions of endocannabinoids, mediated through CB(2) receptors, also appears to contribute to local analgesic effects*." and Fernandez-Ruiz et al[219] noted "*cannabinoids and related compounds (are) a promising new line of research for therapeutic treatment of a variety of conditions, such as brain injury, chronic pain, glaucoma, asthma, cancer and AIDS-associated effects and other pathologies. Motor disorders are another promising field for the therapeutic application of cannabinoid-related compounds, since the control of movement is one of the more relevant physiological roles of*

209 Rosenthal MS, Kleber HD [1999] Making sense of medical marijuana. Proc Assoc Am Physicians 1999 Mar-Apr;111(2):159-65

210 Hollister LE. [2000] An approach to the medical marijuana controversy. Drug Alcohol Depend 58(1-2):3-7

211 Clark PA.[2000] The ethics of medical marijuana: government restrictions vs. medical necessity. J Public Health Policy 2000;21(1):40-60

212 Joy JE, Watson SJ & Benson JA (Eds) (1999) Marijuana and Medicine - assessing the science base. Institute of Medicine Washington DC: National Academy Press p145

213 Pertwee RG, Ross RA. [2002] Cannabinoid receptors and their ligands. Prostaglandins Leukot Essent Fatty Acids. 66(2-3):101-21.

214 Pertwee RG. [2002] Cannabinoids and multiple sclerosis. Pharmacol Ther. 95(2):165-74.

215 Fride E. [2002] Endocannabinoids in the central nervous system--an overview. Prostaglandins Leukot Essent Fatty Acids. 66(2-3):221-33

216 Walker JM, Huang SM. [2002] Endocannabinoids in pain modulation. Prostaglandins Leukot Essent Fatty Acids 66(2-3):235-42

217 Walker JM, Huang SM. [2002] Cannabinoid analgesia. Pharmacol Ther. 95(2):127-35.

218 Rice AS, Farquhar-Smith WP, Nagy I. [2002] Endocannabinoids and pain: spinal and peripheral analgesia in inflammation and neuropathy. Prostaglandins Leukot Essent Fatty Acids. 66(2-3):243-56.

219 Fernandez-Ruiz J, Lastres-Becker I, Cabranes A, Gonzalez S, Ramos JA. [2002] Endocannabinoids and basal ganglia functionality. Prostaglandins Leukot Essent Fatty Acids. 66(2-3):257-67.

the endocannabinoid transmission in the brain. There are two pathologies, Parkinson's disease and Huntington's chorea, which are particularly interesting from a clinical point of view due to the direct relationship of endocannabinoids and their receptors with neurons that degenerate in those disorders." Beaulieu & Rice[220] concluded "*The cannabinoid system is a major target in the treatment of pain and its therapeutic potential should be assessed in the near future by the performance of new clinical trials*." Reviewing pain relief in MS, Smith[221] cautioned "*In the case of pain, most of the available trials suggest that cannabinoids are not superior to existing treatments; however, few trials have examined chronic pain syndromes*" Walker et al[222] observed "*The brain produces at least five compounds that possess sub-micromolar affinity for cannabinoid receptors: anandamide, 2-arachidonoylglycerol, noladin ether, virodhamine, and N-arachidonoyldopamine (NADA). One function of these and/or related compounds is to suppress pain sensitivity. Much evidence supports a role of endocannabinoids in pain modulation in general, and some evidence points to the role of particular endocannabinoids*."

Fowler[223] noted "*the anaesthetic agent propofol and the non-steroidal anti-inflammatory drugs indomethacin and flurbiprofen (when given spinally), activate cannabinoid receptors as an important part of their actions*" Fowler et al[224] later commented "*With respect to the treatment of pain, topical CB1 agonists and CB2 agonists may prove therapeutically useful, and there is evidence that the non-steroidal inflammatory agent indomethacin produces effects secondary to activation of the endocannabinoid system*" and welcomed[225] "*peripherally acting CB agonists and CB2 receptor-selective agonists for the treatment of pain*," Hough et al[226] concluded "*Present and previous studies suggest that Delta(9)-tetrahydrocannabinol may act at both CB(1) and other receptors to relieve pain*"

Grotenhermen[227] commented in 2004 "*Properties of cannabinoids that might be of therapeutic use include analgesia, muscle relaxation, immunosuppression, anti-inflammation, anti-allergic effects, sedation, improvement of mood, stimulation of appetite, anti-emesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects*." In a 2005 review Grotenhermen[228] noted "*Properties of CB receptor agonists that are of therapeutic interest include analgesia, muscle relaxation, immunosuppression, anti-inflammation, antiallergic effects, improvement of mood, stimulation of appetite, antiemesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects. The current main focus of clinical research is their efficacy in chronic pain and neurological disorders. CB receptor antagonists are under investigation for medical use in obesity and nicotine addiction. Additional potential was proposed for the treatment of alcohol and heroine dependency, schizophrenia, conditions with lowered blood pressure, Parkinson's disease and memory impairment in Alzheimer's disease*." Russo concluded[229] "*Migraine, fibromyalgia, IBS and related conditions*

220 Beaulieu P, Rice AS. [2002] [The pharmacology of cannabinoid derivatives: are there applications to treatment of pain?] [Article in French] Ann Fr Anesth Reanim. 21(6):493-508

221 Smith PF [2002] Cannabinoids in the treatment of pain and spasticity in multiple sclerosis. Curr Opin Investig Drugs. 3(6):859-64.

222 Walker JM, Krey JF, Chu CJ, Huang SM. [2002] Endocannabinoids and related fatty acid derivatives in pain modulation. Chem Phys Lipids. 121(1-2):159-72.

223 Fowler CJ. [2004] Possible involvement of the endocannabinoid system in the actions of three clinically used drugs. Trends Pharmacol Sci. 25(2):59-61.

224 Fowler CJ, Holt S, Nilsson O, Jonsson KO, Tiger G, Jacobsson SO. [2005] The endocannabinoid signaling system: pharmacological and therapeutic aspects. Pharmacol Biochem Behav. 81(2):248-62

225 Fowler CJ. [2005] Pharmacological properties and therapeutic possibilities for drugs acting upon endocannabinoid receptors. Curr Drug Targets CNS Neurol Disord. 4(6):685-96.

226 Hough LB, Nalwalk JW, Stadel R, Timmerman H, Leurs R, Paria BC, Wang X, Dey SK. [2002] Inhibition of improgan antinociception by the cannabinoid (CB)(1) antagonist N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (SR141716A): lack of obligatory role for endocannabinoids acting at CB(1) receptors. J Pharmacol Exp Ther. 303(1):314-22.

227 Grotenhermen F. [2004] Pharmacology of cannabinoids. Neuro Endocrinol Lett. 25(1-2):14-23.

228 Grotenhermen F. [2005] Cannabinoids. Curr Drug Targets CNS Neurol Disord. 4(5):507-30.

229 Russo EB. [2004] Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuro Endocrinol Lett. 25(1-2):31-9.

display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines." Martin & Wiley[230] concluded "*The endocannabinoid system has been found to be a key modulator of systems involved in pain perception, emesis, and reward pathways*." Cravatt & Lichtmann[231] concluded "*investigations support a role for endocannabinoids in modulating behavioral responses to acute, inflammatory, and neuropathic pain stimuli.*" Rukwied et al[232] observed "*In clinical studies oral administration of cannabinoids indicated beneficial results during the therapy of multiple sclerosis, weight loss, nausea and vomiting due to chemotherapy, and intractable pruritus. However, therapy of chronic pain conditions revealed conflicting results and unequivocal success could not have been delivered due to unwanted side effects*." Rodriguez de Fonseca et al[233] concluded "*Recent pharmacological advances have led to the synthesis of cannabinoid receptor agonists and antagonists, anandamide uptake blockers and potent, selective inhibitors of endocannabinoid degradation. These new tools have enabled the study of the physiological roles played by the endocannabinoids and have opened up new strategies in the treatment of pain, obesity, neurological diseases including multiple sclerosis, emotional disturbances such as anxiety and other psychiatric disorders including drug addiction*." However, Killestein et al[234] warned "*convincing scientific evidence that cannabinoids are effective in neurological conditions is still lacking. --However, it is also not possible to conclude definitely that cannabinoids are ineffective*"

Bradshaw & Walker[235] noted "*the growing diversity of recently discovered putative lipid mediators and their relationship to the endogenous cannabinoid system. The possibility that there remain many unidentified signalling lipids coupled with the evidence that many of these yield bioactive metabolites due to actions of known enzymes (e.g. cyclooxygenases, lipoxygenases, cytochrome P450s) suggests the existence of a large and complex family of lipid mediators about which only little is known at this time. The elucidation of the biochemistry and pharmacology of these compounds may provide therapeutic targets for a variety of conditions including sleep dysfunction, eating disorders, cardiovascular disease, as well as inflammation and pain*." Schneider et al[236] concluded "*cannabinoids may prove useful in... diseases, e.g. movement disorders such as Gilles de la Tourette's syndrome, multiple sclerosis, and pain*." Corey[237] concluded "*Cannabinoids may be useful for conditions that currently lack effective treatment, such as spasticity, tics and neuropathic pain. New delivery systems for cannabinoids and cannabis-based medicinal extracts, as well as new cannabinoid derivatives expand the options for cannabinoid therapy.*" Radbruch & Elsner[238] noted "*Cannabinoids such as tetrahydrocannabinol offer a valuable add-on option for cancer patients with refractory pain, spasticity, nausea or appetite loss*." In a review of MS research, Malfitano et al[239] concluded "*increase of the circulating levels of endocannabinoids might have a therapeutic effect, and that agonists of endocannabinoids with low psychoactive effects could open new strategies for the treatment of multiple sclerosis*."

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230 Martin BR, Wiley JL. [2004] Mechanism of action of cannabinoids: how it may lead to treatment of cachexia, emesis, and pain. J Support Oncol. 2(4):305-14; discussion 314-6.

231 Cravatt BF, Lichtman AH. [2004] The endogenous cannabinoid system and its role in nociceptive behavior. J Neurobiol. 61(1):149-60.

232 Rukwied R, Gauter B, Schley M, Konrad C. [2005] [Cannabinoids--signal transduction and mode of action] [Article in German] Schmerz. 19(6):528-34.

233 Rodriguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. [2005] The endocannabinoid system: physiology and pharmacology. Alcohol Alcohol. 40(1):2-14.

234 Killestein J, Bet PM, van Loenen AC, Polman CH. [2004] [Medicinal cannabis for diseases of the nervous system: no convincing evidence of effectiveness] [Article in Dutch] Ned Tijdschr Geneeskd. 148(48):2374-8.

235 Bradshaw HB, Walker JM. [2005] The expanding field of cannabimimetic and related lipid mediators. Br J Pharmacol. 144(4):459-65.

236 Schneider U, Seifert J, Karst M, Schlimme J, Cimander K, Muller-Vahl KR. [2005] [The endogenous cannabinoid system. Therapeutic implications for neurologic and psychiatric disorders] [Article in German] Nervenarzt. 76(9):1062, 1065-6, 1068-72 passim.

237 Corey S. [2005] Recent developments in the therapeutic potential of cannabinoids. P R Health Sci J. 24(1):19-26.

238 Radbruch L, Elsner F. [2005] [Palliative pain therapy, cannabinoids] [Article in German] Internist (Berl). 46(10):1105-14.

239 Malfitano AM, Matarese G, Bifulco M. [2005] From cannabis to endocannabinoids in multiple sclerosis: a paradigm of central nervous system autoimmune diseases. Curr Drug Targets CNS Neurol Disord. 4(6):667-75.

Burstein[240] concluded "*(Ajulemic acid) AJA shows efficacy in models for pain and inflammation. Furthermore, in the rat adjuvant arthritis model, it displayed a remarkable action in preventing the destruction of inflamed joints. A phase-2 human trial with chronic, neuropathic pain patients suggested that AJA could become a useful drug for treating this condition.*"

Lynch[241] concluded "*potent antinociceptive and antihyperalgesic effects of cannabinoid agonists in animal models of acute and chronic pain; the presence of cannabinoid receptors in pain-processing areas of the brain, spinal cord and periphery; and evidence supporting endogenous modulation of pain systems by cannabinoids has provided support that cannabinoids exhibit significant potential as analgesics.*" Gourlay[242] concluded "*There is great potential for cannabinoids in the treatment of pain*" Clark et al[243] recommended "*off-label dosing of nabilone… and dronabinol… in the treatment of chronic pain*" Burns & Ineck[244] concluded "*Cannabinoids provide a potential approach to pain management with a novel therapeutic target and mechanism. Chronic pain often requires a polypharmaceutical approach to management, and cannabinoids are a potential addition to the arsenal of treatment options.*" Storr et al[245] observed "*The clinically proven effects in the treatment of pain, cachexia in conjunction with HIV, or malignant disease and treatment of nausea and vomiting in conjunction with chemotherapy now result in the prescription of cannabinoids as valuable medication.*" Azad & Rammes[246] concluded "*the most recent preclinical and clinical data suggest that cannabinoids should be applied as low-dose co-analgesics to inhibit neuroplasticity and central sensitization rather than as analgesics in acute pain*"

Investigating migraine, Cupini et al[247] noted "*in migraineur women an increased AEA (anandamide) degradation by platelets, and hence a reduced concentration of AEA in blood, might reduce the pain threshold and possibly explain the prevalence of migraine in women. The involvement of the endocannabinoid system in migraine is new and broadens our knowledge of this widespread and multifactorial disease.*" Mbvundula et al[248] concluded "*Endocannabinoids naturally reduce pain and are cerebroprotective. Natural and synthetic cannabinoids have the potential to reduce nociception, reverse the development of allodynia and hyperalgesia, reduce inflammation and inflammatory pain and protect from secondary tissue damage in traumatic head injury.*"

Summary

Cannabis contains over 200 chemical compounds, several of which may have a beneficial, or harmful, effect either working alone, or in concert with other compounds. There is now a scientific consensus of the efficacy of THC and other cannabinoids as analgesic (pain relieving) agents. The volume of scientific evidence grows on a daily basis, and several credible mechanisms

240 Burstein S.[2005] Ajulemic acid (IP-751): synthesis, proof of principle, toxicity studies, and clinical trials. AAPS J. 7(1):E143-8.

241 Lynch ME. [2005] Preclinical science regarding cannabinoids as analgesics: An overview. Pain Res Manag. 10 Suppl A:7A-14A.

242 Gourlay D. [2005] Addiction and pain medicine. Pain Res Manag. 10 Suppl A:38A-43A.

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involved in the mediation of pain by external or endogenous cannabonids have been demonstrated, with major implications for the field of neurochemistry as a whole. Cannabinoids appear to modulate the way pain is perceived, regulating the pain threshold, and also increasing the efficacy and duration of action of other pain-relieving drugs. There is evidence suggestive of cannabinoid receptors playing a role in the analgesia from non-steroidal anti-inflammatory drugs such as ibuprofen and paracetamol. The general reduction of muscle tone and specific effects on muscle spasms, indicate cannabis or cannabinoids to have a potential therapeutic role in the management of chronic musculoskeletal and/or visceral pain.

There is an overwhelming body of research, originally historical and/or anecdotal, but supported by a vast number of recent laboratory studies on animal and human models, to demonstrate increased tolerance of pain from administration of cannabis or individual, cannabinoids, including THC. A 'pain-threshold' regulatory area has been found in the rostal ventromedial medulla mediated by cannabinoid receptors, and other researchers have identified roles for cannabinoid analgesia within other areas in the central nervous system and periphery. Walker et al[249] summarised the state of knowledge thus "*Cannabinoids have been used to treat pain for many centuries. However, only during the past several decades have rigorous scientific methods been applied to understand the mechanisms of cannabinoid action. Cannabinoid receptors were discovered in the late 1980s and have been found to mediate the effects of cannabinoids on the nervous system. Several endocannabinoids were subsequently identified. Many studies of cannabinoid analgesia in animals during the past century showed that cannabinoids block all types of pain studied. These effects were found to be due to the suppression of spinal and thalamic nociceptive neurons, independent of any actions on the motor systems. Spinal, supraspinal and peripheral sites of cannabinoid analgesia have been identified. Endocannabinoids are released upon electrical stimulation of the periaqueductal gray, and in response to inflammation in the extremities. These observations and others thus suggest that a natural function of cannabinoid receptors and their endogenous ligands is to regulate pain sensitivity.*"

The 1997 BMA report recommended "*The prescription of Nabilone, THC and other cannabinoids should be permitted for patients with intractable pain. Further research is needed into the potential of cannabidiol*" Clinical trials underway demonstrate cannabinoid extracts to be capable of producing pain relief ranging from moderate to 'life changing', and to reduce the levels of opiate painkillers used by patients.

Research has established a neurochemical mechanism for the action of cannabis (THC), based on a 'cannabis receptor' and an endogenous ligand known as 'anandamide'. The mode of action appears to be the modulation of the responses to incoming stimuli mediated by a 'second messenger' system. The body's natural cannabinoids may be used to 'turn up or down the body's pain thresholds. There is also increasing evidence of anti-inflammatory activity of cannabidiol (CBD).

Clinical trials have had conflicting results, with many studies finding the drug effects not superior to placebo. However the dosages used in such studies tend to be much lower than commonly experienced by recreational drug users, in order to avoid 'unmasking' (subjects becoming aware of the difference between active drug and placebo), or undesirable side effects in the form of a drug 'high'. Studies involving oral THC have proven particularly susceptible to

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adverse effects, whereas sublingual THC/CBD extracts, and novel specific cannabinoids have shown more promising results.

Recent developments have found the endocannabinoid system to be integral to the control of pain whether by opiates or non-steroidal anti-inflammatory drugs or Cox-2 inhibitors. The receptor distribution is widespread in both central nervous system and peripheral tissues. The psychotropic effects limit the use of raw cannabis or THC in non-users of cannabis, who find such effects distressing. Current or former recreational users of cannabis would not generally regard such effects as adverse. The adjunctive use of cannabidiol (CBD) to minimize the psychotropic effects of THC (the high, and also risk of psychotic symptoms) may improve tolerability of treatments among the general population.

More specific drugs acting selectively on peripheral CB-2 receptors, and enzyme inhibitors preventing the breakdown of endocannabinoids offer a potential to separate the analgesic effects from the drug high, and point to a mainstream role of cannabinoid medicines in the management of pain.