



Pain Relief Foundation

Medical Student Essay Competition 2011

Winning Entry

Emily Clarke
Norwich University Medical School

Politics and Pain: The Controversies of Medicinal Cannabinoids

Introduction and History

Over the past century, public perception of cannabis has been at best inconsistent. In the early 1900s cannabis was commonly prescribed for the treatment of a multitude of ailments and afflictions before being radically demoted to an illegal substance 50 years later. The withdrawal of the drug was based upon wide-reaching concern over the potential for abuse, and more recently, the propensity for psychological disturbance. However, over the past 40 years and in the face of much controversy, research has continued, initiating the re-establishment of cannabinoid therapy in UK medicine. In June 2010, a cannabis extract was licensed for muscle spasticity and spasms in multiple sclerosis (MS) but as of yet no derivative has been licensed for chronic pain. This essay aims to discuss the medicinal benefits and short-comings of cannabinoids in order to debate the future use of the drug in the treatment of intractable pain. The question underlying much of the discussion is a simple one: can an illicit drug be used to develop a legal and effective medicine?

For the past 5,000 years cannabis has been undergoing what one may describe as informal 'phase 1 clinical trials', with the first recorded use by the Chinese Emperor Shen Nung in 3700 BC¹. However, the first formal writings on the analgesic properties of cannabis date back to the mid 19th century when Dr O'Shaughnessy and others professed its use in neuralgia, inflammation, neuritis, migraine, spasticity and rheumatism². Indeed, even Queen Victoria was privy to the use of cannabis in the treatment of her dysmenorrhoea. Over the 20th century, the use of cannabis slowly declined in line with the increased use of opiates, benzodiazepines and aspirin, before being labelled a Schedule 1

Drug in 1971². A combination of political and legal issues alongside an absence of medicinal preparations hindered research and professional debate until the very end of the 20th century. However, over the last 10 years there has been a notable surge in cannabinoid research, predominantly driven by a need to alleviate suffering for those patients enduring intractable pain alongside other unpleasant symptoms.

The Endogenous-Cannabinoid System

Cannabis is produced from the plant *Cannabis sativa*. It contains more than 400 compounds, but 66 have so far been identified as cannabinoids, due to their 21 carbon structure and interaction with the endogenous-cannabinoid system³.

The endogenous-cannabinoid system is a neuromodulatory system which helps regulate pain, inflammation, appetite, mood, thermoregulation, circadian rhythm, hormonal function, bone homeostasis and memory. Whilst the system was first discovered in 1988, in evolutionary terms it probably dates back some 600 million years which is indicative of its functional importance.

The system is comprised of two G-protein coupled cannabinoid receptors found on the surface of neurones CB1R and CB2R. CB1R is located within the central and enteric nervous systems as well as several other organs including the uterus, prostate, adrenals, bladder, liver, heart and blood vessels⁴. CB2R is located within the peripheral nervous system, particularly within white blood cells predominantly in the spleen, tonsils and thymus⁴.

Endogenous ligands to CB1R and CB2R have been isolated and are collectively termed 'endocannabinoids'. The first endocannabinoid to be identified was anandamide (also known as N-arachidonylethanolamine, AEA) in 1992, which has been shown to be involved in pain, working memory, embryonic implantation, feeding, motivation and pleasure. Other more recently discovered endocannabinoids include 2-arachidonoyl glycerol (2-AG), 2-arachidonoyl glyceryl ether, N-arachidonoyl-dopamine (NADA) and virodhamine (OAE).

Cannabinoid effect on pain is multi-faceted with actions throughout the peripheral and central nervous systems mainly acting via non-opioid mechanisms. Firstly, mast cells and white blood cells have CB2R embedded in their cell membranes, which when bound by cannabinoids prevents the release of histamine from mast cells, down regulates T cell proliferation, limits leukocyte recruitment and reduces cytokine production^{2, 4}. Secondly, cannabinoids have been found to be implicated in the reduction of primary and secondary hyperalgesia since they inhibit

neurotransmitter release via a multi-step retrograde signalling pathway at the dorsal root ganglion and rostro-ventromedial (RVM) nucleus⁵⁻⁷. Moreover, there are likely to be endocannabinoid receptors more centrally located within the central nervous system (CNS) that have not yet been discovered. Reductions in chronic pain from migraines^{8,9} for instance, suggest that cannabinoids may have a further impact on nociception through unspecified cortical action.

Based on the mechanisms above, it has been suggested that hyperalgesia and chronic pain may be more likely to develop in individuals who suffer from chronically low levels of endogenous cannabinoids due to a reduction in tonic inhibition of pain perception^{2,10}.

Preparations and Indications

There are currently two cannabinoid medicinal preparations licensed for use in the UK. The first to be introduced was Nabilone (Cesamet®) in 1984 for the treatment of chemotherapy induced nausea and vomiting (CINV). It is a synthetic analogue of the exogenous cannabinoid found in *Cannabis sativa*, called delta-9-tetrahydrocannabinol (THC). THC binds to CB1R and CB2R receptors and possesses analgesic, anti-emetic, anti-nausea, anti-spasmodic and appetite-stimulant properties. However, it is also believed to be responsible for the psychotropic effects of cannabis. Nabilone's anti-emetic properties have been largely superseded by 5-HT₃ receptor antagonists, but it is still recommended for patients who fail to achieve adequate control of their chronic pain^{11,12}.

A second preparation was introduced in 2010, licensed for use for spasticity and spasms in MS, with the aim of using another cannabinoid, cannabidiol (CBD), in combination with THC to lessen its psychotropic effects. Unlike THC, CBD is known to possess analgesic, anti-spasmodic, anti-convulsant, anxiolytic and anti-inflammatory properties, as well as being neuroprotective and anti-psychotic. Subsequently, THC:CBD sublingual spray (Sativex®) has achieved far fewer reported psychotropic effects (2.2%)¹³ than Nabilone.

Dronabinol (Marinol®) is a third preparation containing 2.5, 5 or 10mg synthetic THC. It is licensed in the United States as an anti-emetic but is not licensed in the UK.

Efficacy

Recently, the efficacy of cannabinoids in chronic pain has been extensively debated in the literature but with too few underlying randomised controlled trials (RCTs) and systematic reviews to draw definitive conclusions. All evidence thus far has been consistent with THC found to have similar analgesic efficacy to codeine, with a significant dose-related effect superior to placebo^{14, 15}. However, one such systematic review by Campbell et al (2001)¹⁴ concluded that since THC was not any more effective than codeine in the management of chronic pain, widespread use of the drug was not advocated particularly in the treatment of moderate/ severe acute pain. Conversely, Karst et al (2010)¹⁶ stated that patients with intractable pain may benefit from adjuvant cannabinoid therapy since their mechanism of action is largely independent of other agents. This is supported by the work of Cichewicz et al (1999)¹⁷ who noted that opioid anti-nociception is augmented by oral THC and therefore cannabinoids may be best utilised in conjunction with more conventional agents [Appendix 1].

It appears that the debate has progressed from one concerning the 'efficacy' of cannabinoids in chronic pain to a question of 'need' for additional treatments. Neuropathic pain has been highlighted as the type of pain least satisfied by current treatment options. In 1997, National Institute of Health stated that *'available analgesics are, at best, marginally effective'*². A recent systematic review by Lynch et al (2011)¹⁵ and a case-series by Notcutt et al (2004)¹⁸ found that cannabinoids were a reasonable treatment option for neuropathic pain with modest efficacy (median VAS pain reduction; placebo 5.9 (IQR: 2.8-7.3), THC;CBD 4.4 (IQR: 2.6-5.8), $p < 0.001$)¹⁸ and a good safety profile.

Sleep disruption is a further area in which cannabinoids may be of therapeutic value. Chronic pain often causes sleep disturbance which in turn may worsen the perceived pain. Opioids appear counterproductive in this situation since they disrupt sleep architecture, whereas cannabinoids provide significant improvements to sleep¹⁸ [Appendix 2].

A further use may be in the treatment of post-operative pain, since high doses of opiates cause respiratory depression and basal atelectasis as well as nausea and vomiting, resulting in further distress to the patient and the potential for delayed wound healing². Implementing cannabinoids in the treatment of post-operative pain alongside opiates would enable simultaneous use of the drugs anti-emetic and analgesic properties. Campbell et al (2001)¹⁴ however, warns against the sole use of cannabinoids for post-operative pain due to concern over the relatively mild analgesic effect when compared to morphine.

Side Effect Profile

This subject is close to the heart of the ethical and legal dilemmas surrounding the medicalisation of cannabis as many members of the public believe irrefutably that the psychoactive effects of cannabis and its derivatives are responsible for psychosis, addiction, cognitive impairment and death. However, many chronic pain sufferers are unequivocal in their belief that that the psychoactive properties of the drug are beneficial in helping with the increased incidence of concurrent psychological disorders such as depression, psychosis and anxiety^{19,20}.

Concerning psychosis, Aragon et al (2009)²¹ concluded that medicinal doses of Sativex® used in MS patients did not increase the incidence of psychosis and commented that this is likely to be due to the small doses used in clinical settings as compared to recreational doses of THC. In comparison, recreational but non-susceptible adolescent users were subject to a moderate increase the incidence of psychosis, but the risk is dramatically increased for predisposed individuals^{22, 23}. Johns (2001)²⁴ wrote of the minimal likelihood for gross structural brain damage but supported the concept of increased Schizophrenia rates in the susceptible patient. He also documented the amotivational states and intellectual deterioration associated with chronic use.

The subject of addiction and cannabis has also been extensively investigated with 9% of users suffering from dependence, comparing favourably to anxiolytics which carry a 69% addiction rate²⁵. It is commonly believed that dependence on cannabis is of psychological origin involving reinforcement of reward pathways involving the median forebrain bundle and the nucleus accumbens²⁵. Many also admit concern for the propensity for psychologically dependent individuals to convert to stronger agents. Whilst there is undeniably an increased risk for those who use the drug recreationally, it is accepted that this is not a concern for users of medicinal preparations as the initial aim of therapy is pain reduction rather than an illegal 'high'. On the other hand, Georgotas and Zeidenberg (1979)²⁶ noted a reduction in the perceived strength of cannabis following administration of inhaled 210mg THC daily for four weeks, with reports of irritation and hostility over 3 weeks post-cessation. It should be noted though that tolerance and dependence are normal physiological adaptations to many drugs²⁵ acting on the CNS and since 210mg is a very high dose of a psychotropic cannabinoid; these effects are unlikely to be as severe in medicinal preparations.

Over the past 5,000 years there have been no recorded deaths directly due to cannabis/ cannabinoid overdose. Yassa et al (2010)²⁷ calculated the LD50 (Lethal Dose 50%) of THC in male rats as 1,270mg/kg, which if extrapolated to humans would require consumption of approximately 30,000 marijuana cigarettes. This high LD50 is very reassuring but it must be remembered that, although

cannabis has never independently caused death, it can cause a delayed motor response that could potentially cause road traffic accidents. It has been identified in blood samples at many post-mortems but always alongside other agents such as alcohol and other recreational drugs. The safety of drugs however is best appreciated when compared to other commonly used medications. Blower et al (1997)²⁸ estimated the number of UK Non-Steroidal Anti-Inflammatory Drug (NSAID)-associated emergency admissions as approximately 12,000 with 2,500 deaths per year. Similarly the 1998 Home Office Bulletin stated that 1,602 deaths and 683 suicides were directly related to benzodiazepine use.

To conclude, the side-effect profile of medicinal preparations of cannabis is reassuringly mild especially when compared to other agents freely available for use. Recreational use of the drug is not as safe most likely due to the differing personality types of users, usage aims and higher dosage.

Funding

Sadly funding is a big consideration in a national health service where there are finite resources but almost infinite need. Regrettably both Nabilone[®] and Sativex[®] are very expensive agents, limiting prescription drastically.

Nabilone[®] is now no longer under patent yet its continued high cost (approximately £10 per day for 2 x 1mg capsules) limits funding by Primary Care Trusts. Sativex[®] on the other hand is still on patent but is unfunded by the NHS; patients using the drug include only those who were involved with clinical trials alongside those who are self funding (£125 per 10ml vial = approximately £11 per day).

Legality and Social Debate

Currently in the UK it is illegal to possess or sell recreational cannabis due to its Schedule 1 status under the Misuse of Drugs Regulations (2001). Prescribed medicinal preparations have recently been amended from a Schedule 4 drug, alongside benzodiazepines and steroids, to a Schedule 2 status, alongside diamorphine, morphine, methadone, pethidine and cocaine. Schedule 1 drugs are prohibited since they are considered to have virtually no therapeutic use, Schedule 2 agents are controlled drugs that require a licence for import and exportation and must be kept in a locked cabinet/ safe, whereas Schedule 4 medicines are not subject to safe custody requirements.

Despite Meek et al (1994)²⁹ demonstrating that 75% of British doctors would like cannabis to be available on prescription, many physicians openly admit to being reluctant to prescribe medicinal preparations. This is most likely due to the high cost of the drug in combination with its contentious nature, exacerbated undoubtedly by its new Schedule 2 status. Consequently many patients are openly admitting to physicians that they are purchasing cannabis illegally in order to relieve their suffering³⁰. This situation is obviously far from ideal, as otherwise law-abiding citizens are feeling compelled into illegal and dangerous interactions with criminals whilst also risking prosecution. Moreover, patients cannot be sure of the purity or the amount that they are receiving and subsequently they may fall prey to harmful side-effects.

There have been numerous legal cases in the UK concerning prosecution of legitimate chronic pain sufferers using illegal preparations of cannabis, with some individuals acquitted under medical necessity (Duress of Circumstance). Those who have been exonerated proved that their use of non-medicinal cannabis avoided death or serious injury (psychological or physical); whereas those who were prosecuted failed to prove that their actions prevented a 'greater evil'.

It is difficult not to view these cases as a convincing argument for the licensing of cannabinoids in chronic pain. In the words of Judge Mark Polen; *'To ignore the plight of such people renders the law callous to the most basic of human rights: the right to self-preservation'*.¹

Conclusion

After a thorough review of the evidence for and against the medicalisation of cannabinoids, it is difficult to ignore the potential use of the drug in the treatment of intractable pain. The incidence of chronic pain is rising with more than 1 in 12 people affected, most likely due to a combination of changing attitudes towards pain alongside an ageing population. The focus in healthcare has also shifted, with new found appreciation for quality of life over quantity and therefore it is difficult to find cause for not-licensing any agent that is deemed effective and safe. The existing evidence speaks for itself in these terms; many systematic reviews have found cannabinoids to be equally as effective as commonly prescribed opioids^{14, 15}. However, whilst there has been a recent surge in cannabinoid research, the results of many more high-quality RCTs are required before definitive conclusions can be drawn. In terms of safety, the illegal agent from which it is derived has never directly caused death whilst the side-effects at medicinal doses are minimal. Indeed the contentious yet potentially beneficial psychotropic effect of cannabis has been largely removed through the introduction of cannabidiol. Given the expense of these agents, however, it is reasonable that

cannabinoids should remain a last resort in pain therapy. However, it is unfortunate that in the situation of intractable pain funding remains unavailable, rendering the drug inaccessible for the vast majority of patients.

Over the course of researching this essay, it has become apparent how closely medicinal cannabinoids are often believed to be synonymous with illegal preparations. This paradigm is unique to cannabinoids, since very few people seem to associate codeine with opium and diamorphine with heroin. It is unlikely that medicinal 'cannabinoids' will be viewed independently from its illegal counterpart 'cannabis', without conscious differentiation by nomenclature, law, society and medical practitioners. Until this occurs, it is possible that the true benefits of the drug will not be fairly assessed or fully realised.

References

1. Mathre, M.L. *Cannabis in Medical Practice: A legal, Historical and Pharmacological Overview of the Therapeutic Use of Marijuana*. 1997, McFarland & Company.
2. Guy, G.W., Whittle, B.A., Robson, P.J. *The Medicinal Uses of Cannabis and Cannabinoids*. 2004, Pharmaceutical Press.
3. Davison, S.N., Davison, J.S. *Special Article: Is There a Legitimate Role for the Therapeutic Use of Cannabinoids for Symptom Management in Chronic Kidney Disease?* *Journal of Pain & Symptom Management*, 2011. **41**(4): p. 768-778.
4. Basavarajappa, B.S. *Neuropharmacology of the endocannabinoid signaling system - molecular mechanisms, biological actions and synaptic plasticity*. *Current Neuropharmacology*, 2007. **5**: p. 81-97.
5. Johaneck, S.I., Heitmiller, D., Turner, M., Nader, N., Hodges, J., Simone, D. *Cannabinoids attenuate capsaicin-evoked hyperalgesia through spinal and peripheral mechanisms*. *Pain*, 2001. **93**: p. 303-315.
6. Jagger, S.I., Sellaturay, S., Rice, A.S. *The endogenous cannabinoid anandamide, but not the CB2 ligand palmitoylethanolamide, prevents viscerovisceral hyper-reflexia associated with inflammation of the rat urinary bladder*. *Neuroscience*, 1998. **253**: p. 123-126.
7. Millns, P.J., Chapman, V., Kendall, D.A. *Cannabinoid inhibition of the capsaicin-induced calcium response in rat dorsal root ganglion neurones*. *Pharmacology*, 2001. **132**: p. 969-971.
8. Cupini, L.M., Costa, C., Sarchielli, P., Bari, M., Battista, N., Eusebi, P., Calabresi, P., Maccarrone, M. *Degradation of endocannabinoids in chronic migraine and medication overuse headache*. *Neurobiology*, 2008. **30**(2): p. 186-9.
9. Volfe, Z., Dvilansky, A. and Nathan, I. *Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients*. *International Journal Clinical Pharmacological Research*, 1985. **5**(4): p. 243-6.
10. Russo, E.B. *Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?* *Neuroendocrinology*, 2008. **29**(2): p. 192-200.
11. Ware, M.A., Daeninck, P., Maida, V. *A review of nabilone in the treatment of chemotherapy-induced nausea and vomiting*. *Therapeutics and Clinical Risk Management*, 2008. **4**(1): p. 99-107.
12. Notcutt, W., Rocket, M., Zajicek, J., Muthusamy, K. *A Retrospective Description of the use of Nabilone in UK Clinical Practice*, in *British Pain Society Annual Scientific Meeting*. 2011

13. Robson, R. *Abuse potential and psychoactive effects of δ -9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine*. Expert Opinion on Drug Safety, 2011. [In print].
14. Campbell, F.A., Tramèr, M.R., Carroll, D., Reynolds, D.J., Moore, R.A., McQuay, H.J. *Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review*. British Medical Journal, 2001. **323**(7303): p. 13-6.
15. Lynch, M.E., Campbell, F. *Cannabinoids for Treatment of Chronic Non-Cancer Pain; a Systematic Review of Randomized Trials*. British Journal of Clinical Pharmacology, 2011. [In Print].
16. Karst, M., Wippermann, S., Ahrens, J. *Role of cannabinoids in the treatment of pain and (painful) spasticity*. Drugs, 2010. **70**(18): p. 2409-38.
17. Cichewicz, D.L., Martin, Z.L., Smith, F.L., Welch, S.P., *Enhancement of μ Opioid Antinociception by Oral Δ 9-Tetrahydrocannabinol: Dose-Response Analysis and Receptor Identification*. The Journal of Pharmacology and Experimental Therapeutics, 1999. **289**: p. 859-867.
18. Notcutt, W., Price, M., Miller, R., Newport, S., Phillips, C., Simmons, S., Sansom, C. *Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies*. Anaesthesia, 2004. **59**(5): p. 440-52.
19. Feinstein, A. *Multiple Sclerosis, depression and suicide. Clinicians should pay more attention to psychopathology*. Editorial British Medical Journal, 1997. **315**: p. 691-692.
20. Ramage-Morin, P.L., Gilmour, H. *Chronic pain at ages 12 to 44*. Health Reports, 2010. **21**(4): p. 53-61.
21. Aragona, M., Onesti, E., Tomassini, V., Conte, A., Gupta, S., Gilio, F., Pantano, P., Pozzilli, C., Inghilleri, M. *Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study*. Clinical Neuropharmacology, 2009. **32**(1): p. 41-7.
22. Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H.U., van Os, J. *Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people*. British Medical Journal, 2005. **330**(7481): p. 11.
23. Degenhardt, L., Hall, W. *Cannabis and psychosis*. Current Psychiatric Reports, 2002. **4**: p. 191-196.
24. Johns, A. *Psychiatric effects of cannabis*. The British Journal of Psychiatry 2001. **178**: p. 116-122.

25. Joy, J.E., Watson, S.J., Benson, J.A., *Marijuana and Medicine: Assessing the Science Base*. Institute of Medicine, 1999. National Academy Press.
26. Georgotas, A., Zeidenberg, P. *Observations on the effects of four weeks of heavy marijuana smoking on group interaction and individual behaviour*. *Comprehensive Psychiatry*, 1979. **20**(5): p. 427-32.
27. Yassa, H.A., Dawood Ael, W., Shehata, M.M., Abdel-Hady, R.H., Aal, K.M. *Subchronic toxicity of cannabis leaves on male albino rats*. *Human and Experimental Toxicology*, 2010. **29**(1): p. 37-47.
28. Blower, A.L., Brooks, A., Fenn, C.G. *Emergency admissions for upper gastrointestinal disease and their relation to NSAID use*. *Alimentary Pharmacology and Therapeutics*, 1997. **11**: p. 283-91.
29. Meek, C. *Doctors want cannabis prescriptions allowed*. *British Medical Association News Review*, 1994(February): p. 1-19.
30. Cannazine Cannabis News. *Cannabis Medicine Backed by Respected Irish Consultant Neurologist*, 2011. <http://pr.cannazine.co.uk/201106061462/green/eco-news/cannabis-medicine-backed-by-respected-irish-consultant-neurologist.html> [cited 19/6/2011].

Appendix 1: Cannabinoids Enhance Opioid Antinociception

Reproduced from: Cichewicz, D.L., Martin, Z.L., Smith, F.L. and Welch, S.P., *Enhancement of μ Opioid Antinociception by Oral Δ^9 -Tetrahydrocannabinol: Dose-Response Analysis and Receptor Identification*. The Journal of Pharmacology and Experimental Therapeutics, 1999. **289**: p. 859-867.

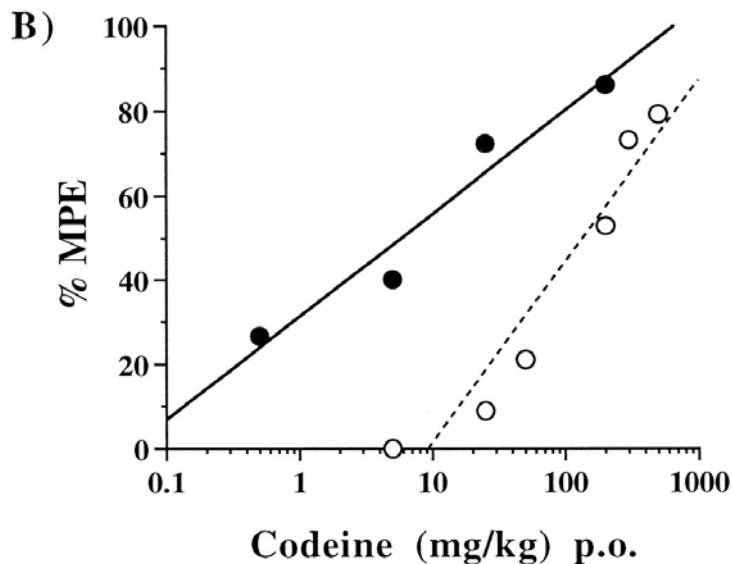
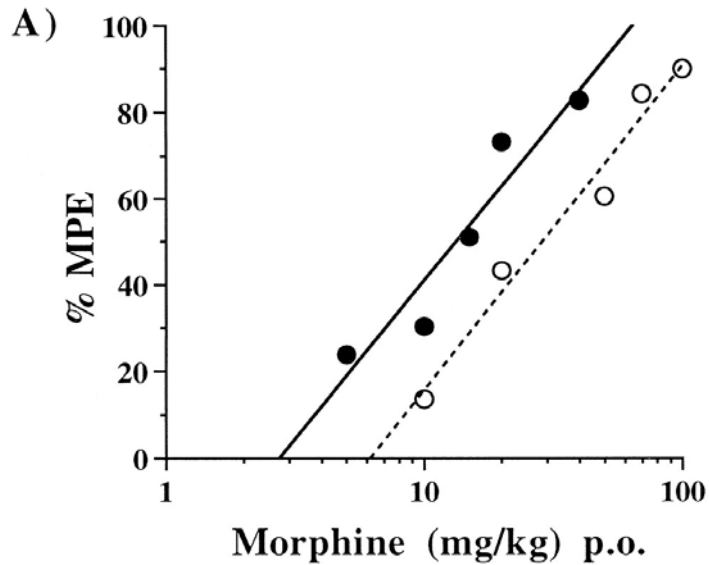


Figure. The antinociceptive effects of morphine and codeine are enhanced by Δ^9 -THC. Vehicle (1:1:18) or Δ^9 -THC at an inactive dose of 20 mg/kg was administered to mice p.o. 15 min before morphine p.o. (A) or 30 min before codeine p.o. (B). The animals were tested 30 min later in the tail-flick test. The data are presented as % MPE with each data point representing data from five to seven mice. Both 1:1:18 vehicle and distilled water produced no antinociceptive effects. \circ , vehicle pretreatment; \bullet , Δ^9 -THC pretreatment. %MPE = percentage maximal possible effect.

Appendix 2: Cannabinoid Analgesic Effect and Sleep Improvement

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

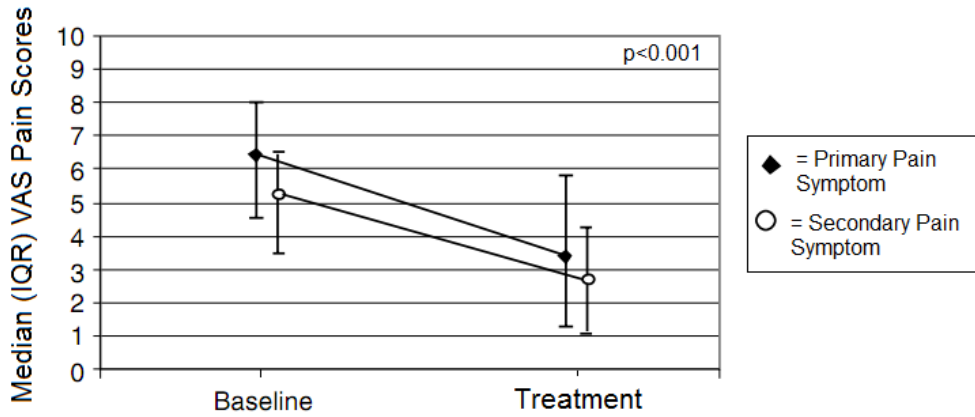


Figure 3 Change in median (interquartile range) VAS for symptom S1 & S2 recorded at the start (baseline) and at completion of the 2-week run-in period for 34 patients with open-label THC : CBD.

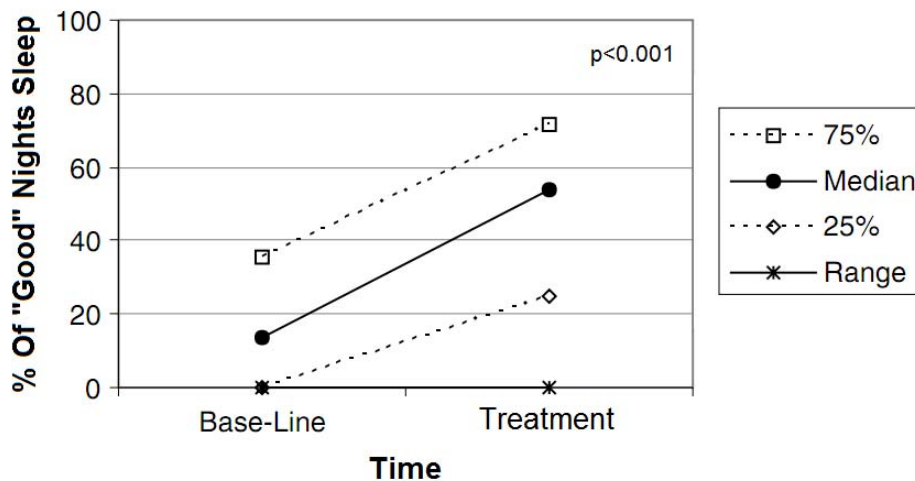


Figure 6 Percentage of nights when sleep was of "good" quality for 32 patients (#3 to #34) comparing the 14-day baseline and run-in periods (median, interquartile range, range).