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Cannabinoids and Neuropathic Pain

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1. Introduction

Cannabinoids are drugs that are either derived from cannabis or that induce similar behavioural and physiological effects to cannabis. They fall into three classes: those that are produced by plants of the *Cannabis* genus, termed phytocannabinoids (plant cannabinoids); those that are produced within the body, termed endocannabinoids (endogenous cannabinoids); and those that are produced synthetically to mimic the pharmacology of naturally occurring cannabinoids.

Cannabinoids stand in relation to cannabis as opioids such as codeine, pethidine, fentanyl, and methadone stand in relation to opium. While opium and opioids are used and abused recreationally, opioids have long been at the forefront of first line analgesia for acute and chronic pain indications. Similarly, while cannabis and synthetic analogues are drugs of abuse, cannabinoids also have beneficial therapeutic effects. While the therapeutic effects of cannabinoids do not yet approach those of opioids, there has been extensive pharmaceutical research into the use of cannabinoids for the treatment of pain. In contrast with opioids, however, there is mounting evidence that cannabinoids may be more efficacious in the treatment of chronic pain conditions, such as neuropathies, rather than acute pain.

2. Cannabinoid pharmacology

2.1 A brief history

Phytocannabinoids are derived from the *Cannabis* species, primarily *Cannabis sativa* which originated in China and Central and South Asia. Two other species are known; *C. indica* and *C. Ruderalis*, and possibly a third; *C. afghanica*. Of these, *C. sativa* is the largest and most diverse genus (Clarke *et al.*, 2002). Cannabis was probably first used as a medicinal herb in India around 800BC, and in Persia and Tibet by 500BC, purportedly as an anaesthetic during surgery, while the therapeutic properties of cannabis were first recorded in China as early as 200 AD. It wasn't until the nineteenth century, however, that the Irish doctor William O'Shaughnessy began the scientific investigation of the chemical properties of cannabis (Frankhauser, 2002).

By 1900 various pharmaceutical companies in Europe were promoting cannabis based products for the treatment of migraine, menstrual cramps, whooping cough, asthma, and as a sedative and soporific. During the twentieth century, however, cannabis lost favor as a medicine due to combination of the development of better drugs, the instability of cannabis

drug formulations, unfavorable economics, and legal restrictions on its availability (Frankhauser, 2002). Today, cannabis and cannabinoids are once again the subject of serious pharmaceutical development. More targeted drug formulations, a greater understanding of the evidence base for cannabinoid efficacy and safety for particular conditions, and the development of wholly new ways of manipulating the endocannabinoid system have lead to a resurgence of research.

Following the initiation of the scientific study of cannabinoid chemistry in 1838 by O'Shaughnessy (Di Marzo, 2006a), the first purified cannabinoid, named cannabinol, was isolated in 1899, and by 1932, its structure had been partially described. In 1964 Raphael Mechoulam, at Hebrew University in Israel, described the structure of the principle pharmacologically active component of cannabis, delta-9-tetrahydrocannabinol (THC) (Mechoulam *et al.*, 1965). Following this critical discovery, the study of the pharmacological effects of cannabis and cannabinoids accelerated from 1970 through to the 1990s. This period of cannabinoid pharmacology clarified the behavioural and physiological effects of cannabis and classical cannabinoids, in particular THC.

It had already been discovered that opium derived opioids interact with an endogenous receptor system, mimicking the actions of endogenous opioids. It was hypothesised that a similar receptor binding system might underlie the effects of cannabinoids, and in 1988, Devane and colleagues (Devane et al., 1988) published an article describing and characterising binding sites for THC. This rapidly led to the discovery of a specific cannabinoid receptor, subsequently termed cannabinoid receptor I, or CB1, in 1990 (Herkenham *et al.*, 1990a). A seminal study by Herkenham and colleagues (Herkenham *et al.*, 1990a) used autoradiographical binding to describe the distribution of CB1 receptors throughout the rat brain. Soon afterward, a similar distribution of CB1 receptors was described for the human brain by Glass and colleagues (Glass et al., 1997). The results of these studies helped explain many of the psychoactive effects of cannabinoids that had been previously characterized.

The discovery of the CB1 receptor gave impetus to the search for endogenous cannabinoids for which CB1 would be the natural target. The first endogenous ligand discovered and characterised for this receptor was a lipid, arachidonoylethanolamide, discovered in 1992, and given the name anandamide after the Sanskrit word for bliss, *ananda* (Devane et al., 1992). Anandamide is not stored in vesicles like classical neurotransmitters, and is instead synthesized in neurons on demand primarily via a two step reaction, catalysed by N-acyltransferase and a member of the phospholipase D family, N-acylphosphatidylethanolamine (Okamoto et al., 2007). It is a highly lipophilic derivative of arachidonic acid and readily diffuses across the plasma membrane upon synthesis, activating CB1 receptors before rapid enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996). This makes anandamide ideally adapted for signaling pathways that require a rapid and local response, such as the regulation of neuronal excitability in the brain, or the modulation of vascular tone. A second endocannabinoid, 2-arachodonalglycerol (2-AG), was discovered in 1995 (Mechoulam et al., 1995). Like anandamide, synthesis and degradation of 2-AG is enzymatically regulated, in this instance primarily by diacylglycerol lipase α and β, and monoglyceride lipase (Dinh et al., 2002), respectively. More recently there have been at least four additional endocannabinoids suggested: 2-arachidonyl-glycerolether (noladin, 2-AGE), *O*-arachidonyl-ethanolamine

(virohdamine), *N*-arachidonoyl-dopamine (NADA) (Pacher et al., 2006), and the sleep inducing oleic acid derivative oleamide (Lees *et al.*, 2004), although these have not been as extensively characterized as anandamide and 2-AG.

A second cannabinoid receptor, cannabinoid receptor II (CB2), was discovered in 1992 (Munro et al., 1993). Unlike CB1, CB2 appeared to be abundant in immune cells of the spleen (lymphocytes) and tonsils but not in the brain (Galiegue, 1995). This finding helped explain another of the pharmacological effects of cannabis; suppression of the immune system.

2.2 Cannabinoid receptors

CB1 occurs in deuterostome invertebrate animals as well as in vertebrates, which suggests that the endocannabinoid system developed early in evolutionary history and is therefore likely to be fundamental to a variety of basic physiological processes (Elphick *et al.*, 2001). These include processes that are mainly involved with both the central and peripheral nervous systems, though CB1 is most densely expressed in the central nervous system (CNS). In addition to the psychoactive effects of CB1 activation in the brain, CB1 receptors have a number of functions in other organ systems. CB1 is co-expressed with CB2 in many immune cells, including monocytes and microglia. Some researchers have suggested that CB1 may be constitutively expressed in immune cells, and respond to initial injury signals, and that a second receptor, CB2, is induced during inflammation or immune functions (Cabral *et al.*, 2005). CB1 receptors are in fact expressed in a great many tissues throughout the body, including in the eye (where they help regulate intraocular pressure), the placenta, gonads and reproductive system, skin, and in nerves terminating in the gut wall (Izzo *et al.*, 2001; Park *et al.*, 2003; Njie *et al.*, 2006). There are also CB1 receptors in cardiac muscle, blood vessels, and on peripheral nerves of the cardiovascular system.

CB2 was characterized shortly after CB1 (Munro et al., 1993). CB2 receptors are found at the highest densities in immune cells, and as such, spleen and tonsil homogenates show very high levels of CB2 protein. For this reason, CB2 has come to be referred to as the cannabinoid immune receptor, contrasting with CB1 as the cannabinoid central nervous system receptor. There are exceptions to this however: as noted CB1 is found in a variety of tissues including immune cells, and CB2 has been found to be important in the proliferation and differentiation of immature neurons. Because CB2 is located for the most part in peripheral tissues and in immune cells in particular, CB2 represents an attractive target for the immunomodulatory and anti-inflammatory effects of cannabinoids, but without the psychoactive effects caused by CB1 activation.

Although CB2 expression is well characterized in the immune system (Galiegue et al., 1995), the expression of the CB2 receptor in the brain is still an area of controversy. It is known now that CB2 are definitely expressed in microglia, which are resident immune cells in the CNS (Cabral *et al.*, 2005). CB2 has been detected in microglia in neuritic plaques in brains taken from patients that have died with Alzheimer's disease (Benito et al., 2003). More controversially, CB2 receptors have also been reported on neurons of rodents and mustelids (Van Sickle *et al.*, 2005; Gong *et al.*, 2006; Onaivi *et al.*, 2006).

CB1 and CB2 are G protein coupled receptors (GPCRs), linked to inhibitory Gi proteins. Activation of these receptors inhibits the accumulation of the messenger molecule cyclic adenosine monophosphate (cAMP) in cells, via inhibition of adenylyl cyclase (Scotter et al.,

2006). GPCRs are extremely abundant and variable, but share the same basic structure; which is an extracellular N terminus, an intracellular C terminus, seven hydrophobic trans-plasma membrane helical domains, three extracellular loops, and three intracellular loops. Cellular signalling pathways for CB1 are well studied; less so for CB2. Stimulation of the CB1 receptor inhibits the influx of Ca^{2+} into cells by way of a variety of voltage sensitive Ca^{2+} channels (VSCCs). In the brain, depolarization of postsynaptic neurons can cause a release of endocannabinoids that act as reverse neurotransmitters to presynaptic CB1 receptors, reducing neurotransmitter release from presynaptic neurons. As CB1 receptors are present on both excitatory and inhibitory neurons, its activation can have diverse and often opposing effects in the central nervous system. CB1 is also coupled to G protein-coupled inwardly rectifying potassium channels (GIRKs), and this tends to hyperpolarize presynaptic neuron terminals, and contributes to the reduction in excitation/inhibition of post-synaptic neurons. Inhibition of VSCCs has also been implicated as a key mechanism by which vascular CB1 receptors mediate vasodilation.

It is important to remember that much of the research that has been done on cannabinoid receptors has been done on those found in rodents, particularly rats. The amino acid sequence for CB1 is very similar in rats and humans, with 97% sequence identity between the two species (Gerard et al., 1991). Although CB1 is highly conserved between species, the same cannot be said for CB2. CB2 has diverged a great deal more between species than CB1, with only 81% sequence identity between the rat and human receptors (Griffin et al., 2000). Modeling the receptors has shown that there is some 87% identity between the rat and human receptors in the transmembrane regions, which are critical for drug binding. Therefore, although CB1 rat models are often (but not always) good predictors of how a drug will perform for human CB1 receptors, this is not so frequently the case for CB2. Drugs that show promising selectivity for CB2 that have only been tested in rodents should therefore be treated with caution when extrapolating possible effects in humans.

While CB1 and CB2 are two undisputed and well characterised members of the cannabinoid receptor family by which cannabinoids exert their effects, there is evidence of cannabinoid binding to additional targets. Some effects by cannabinoids in experiments do not appear to be mediated by either CB1 or CB2. In particular, the endocannabinoid anandamide may act on a variety of targets including a number of orphaned GPCRs (such GPR55, GPR112) T-type Ca^{2+} channels, Na^{2+} channels, Transient Receptor Potential Vanilloid type 1 (TRPV1) channels, α7-nicotinic acetylcholine receptors, and background and voltage-gated K^{+} channels (van der Stelt *et al.*, 2005).

Although cannabinoid analgesia has been reasonably well studied in humans (Pertwee, 2001; Burns *et al.*, 2006; Huskey, 2006; Manzanares *et al.*, 2006) the exact contributions of the cannabinoid receptors is still under investigation. Many preclinical studies have shown that cannabinoids produce analgesia by acting in both the central and peripheral nervous system (Pertwee, 2001), via CB1 receptors in the brain, but also by both CB1 and CB2 receptors in the spinal cord and periphery (Agarwal et al., 2007).

2.3 Cannabinoids

Cannabinoids tend to fall into five major structural classes: The classical cannabinoids (including phytocannabinoids), bicyclic and tricyclic analogues, endocannabinoids,

aminoalkylindoles, and diarylpyrazoles. While classical cannabinoids are based on the structure of phytocannabinoids, the other four classes of ligand are not, and tend to have a non-classical structure.

The first classical cannabinoids were the phytocannabinoids purified from the cannabis plant, *C.sativa*. At least 483 different natural chemicals have been extracted and purifed from cannabis and of these, phytocannabinoids are exclusively found in cannabis plants. At the time of writing, 66 distinct phytocannabinoids have been isolated and purified from *C.sativa*. These include THC and cannabidiol, which have been extensively studied for their medicinal qualities. Dronabinol is the name given to the synthetically produced (-)-*trans*-isomer of THC (which is also naturally occurring), while nabilone, also a classical cannabinoid, is a synthetically produced potent analogue of THC. Both dronabinol and nabilone are currently licensed medications, and are discussed later.

With the characterisation of specific cannabinoid receptors, it was possible to develop synthetic compounds tailored directly to the cannabinoid receptors, which differed from the classical cannabinoid structure. Bicyclic and tricyclic synthetic cannabinoids of the non-classical type make up the second group of cannabinoid ligands. Chief among agonists of this group, CP55,940 was developed by Pfizer in 1974, and is a bicyclic cannabinoid, without the middle dihydropyran ring of the classical tricyclic cannabinoids. These were altered further by the substitution of additional hydroxyl groups for added capability to form hydrogen bonds. CP55,940 is considerably more potent as an agonist at both cannabinoid receptors compared with THC. As a result, the psychoactive effects of CP55,940 are far more intense than those caused by THC (which is a relatively weak cannabinoid receptor agonist) and therefore CP55,940 has not been suitable for clinical use. Unlike dronabinol and nabilone, CP55,940 and other drugs like it have never been marketed because they are extremely psychoactive (i.e., cause profound effects on the central nervous system).

Levonantradol is a tricyclic cannabinoid that was produced by Pfizer, and differs from THC not only in that it has additional hydrogen binding sites, but also in that it has an aromatic group attached to the alkyl tail. Levonantradol is considerably more potent than THC, and unlike CP55,940, was used in clinical tests. Levonantradol was found to provide considerable pain relief for patients after operations, but had more intense side effects than THC (Jain et al., 1981). Another potent tricyclic THC analogue that has been used extensively in studying the endocannabinoid system is HU-210. With a long duration of action, and exhibiting 100-800 times more potency than THC, it is unsuitable for human use. Like other potent synthetic cannabinoids HU-210 has a high degree of oxygen substitution compared with phytocannabinoids. Ajulemic acid is compound that is related to HU-210, and is a synthetic derivative of the active metabolite of THC, 11-carboxy-THC. Ajulemic acid is similar in structure to HU-210, but has a carboxylate substituted for the methyl hydroxyl substituent at position 9. Ajulemic acid has been administered to humans in clinical tests, and has been found to have promise for the control of neuropathic pain.

Synthetic cannabinoids were initially developed based on the classical cannabinoid structural template (Di Marzo, 2006b). Phytocannabinoids are highly lipophilic and show extremely high levels of non-specific binding in radio-ligand binding experiments. Highly potent synthetic analogues of THC are often more polar than phytocannabinoids, and able to form more hydrogen bonds. Because THC and its derivatives tend to be highly lipophilic,

it accumulates in cell membranes when it is applied to sectioned or homogenised tissues. For many years, this made it difficult to identify and characterise the specific binding sites for cannabinoids, which hindered study of the endocannabinoid system. Identification of cannabinoid receptors and their distribution in the body has been greatly facilitated by the discovery of high affinity compounds such as CP 55,940. Radio-labeled CP 55,940 was the compound used by Devane and colleagues (Devane et al., 1988) in the breakthrough work that lead to the characterisation CB1, and by Herkenham and colleagues to describe the distribution of CB1 in the rat brain (Herkenham *et al.*, 1990b).

A third group of cannabinoids consists of endocannabinoids, which were first identified soon after the characterisation of cannabinoid receptors (Di Marzo, 2006b). The prototypical endocannabinoid is anandamide and has been extensively studied for both its biochemistry and pharmacology. Anandamide consists of a long hydrophobic alkyl tail, and an ethanolamide head group. The endocannabinoid 2-AG differs from anandamide by the addition of a second hydroxyl at the headgroup, and an ester group replacing the amide. Anandamide appears to have several-fold greater potency than 2-AG, though there is enormous variation in published results.

A fourth category of cannabinoids, bearing little structural similarity to either classical cannabinoids or endocannabinoids are aminoalkylindoles, the most commonly used of which is WIN55,212-2, which is a potent agonist at both CB1 and CB2 receptors, but shows some degree of selectivity for CB2. JWH-133 is another potent indole that is part of a family of compounds named after their discoverer, JW Huffman, and shows a high degree of selectivity (200-fold) for CB2 (Huffman, 2005).

Non-classical ligand development also included, for the first time, receptor subtype selective antagonists. Developed by Sanofi-Recherche in the 1990s, SR141716A (later SR141716) and SR144528 are highly selective antagonists against CB1 and CB2, respectively, and are members of the fifth main category of cannabinoids, the diarylpyrazoles (Rinaldi-Carmona et al., 1994). By virtue of selectively excluding the actions of one of the cannabinoid receptors, these two compounds have been instrumental in critical research that has furthered our understanding of cannabinoid pharmacology. Indeed these agonists were used to provide definitive evidence that CP 55,940 causes its effects through the same biochemical pathways as THC, in experiments that show that its psychoactive effects are completely blocked by the CB1 receptor antagonist SR141716 (Compton et al., 1992).

Knowledge of receptor selectivity is important for the medicinal use of cannabinoids because CB1 and CB2 have distinct distributions and distinct physiological effects; CB1 is chiefly responsible for the psychoactive effects of cannabinoids and CB2 is mainly involved in the anti-inflammatory and immunomodulatory effects of cannabinoids. Development of subtype selective ligands will be discussed in a later chapter.

3. Cannabis and cannabinoids in the clinic

3.1 Cannabis

Most of the higher quality evidence for the antinociceptive effects of cannabinoids in humans comes from studies using licensed cannabinoid drugs, rather than with medical cannabis. Very few clinical trial data for smoked cannabis exist, though there are some for

HIV-induced neuropathy (Abrams et al., 2007) and experimental pain (Hill *et al.*, 1974; Wallace *et al.*, 2007). It is also difficult to interpret case histories and patient or doctor testimonies, mostly because of the lack of placebo controls, but also because habitual cannabis users can develop tolerance to many of the effects of the drug. Moreover, the amount of active cannabinoids in any given cannabis cigarette is highly variable: THC content in raw cannabis often ranges between 1.5 and 3.7%; the size of the cannabis cigarettes can vary; and the amount of cigarette smoked at any one time can vary.

3.2 Licensed formulations

The cannabinoid drugs that were first approved for clinical use were synthetic analogues or stereoisomers of THC. These are the (-)-*trans*-isomer of THC, dronabinol (Marinol™, Namisol®), and the more potent THC analogue, nabilone (Cesamet™). Both dronabinol and nabilone are used clinically in several countries, especially in palliative care. This abstracts from the ability of cannabis to reduce nausea and vomiting after treatment with anti-cancer medicines (Machado Rocha et al., 2008). There is good evidence and justification for the continued use of cannabinoids in the treatment of nausea and vomiting in patients receiving chemotherapy, especially in those patients whose nausea and emesis does not respond to other treatments. In addition to anti-emetic action, they are also used as appetite stimulants in wasting conditions such as HIV/AIDS. Another THC analogue, levonantradol, has both anti-emetic and powerful analgesic properties. It was effective in the treatment of post surgical pain (Jain et al., 1981), and as an antiemetic in cancer patients (Cronin *et al.*, 1981; Hutcheon *et al.*, 1983; Stambaugh *et al.*, 1984). However, adverse events were common, and sometimes severe and dose limiting (Cronin *et al.*, 1981; Hutcheon *et al.*, 1983), thus the drug was judged unacceptable and the programme was dropped (Dr K. Koe quoted in (Iversen, 2000)).

Marinol is an oral form of dronabinol that is manufactured by Unimed Pharmaceuticals, and is available in the United States, Canada, and in some European countries. Marinol comes as capsules with the dronabinol dissolved in sesame seed oil. These are available in sizes of 2.5, 5 and 10 mg. In an effort to improve the pharmacokinetic profile of orally administered dronabinol, Echo Pharmaceuticals in The Netherlands has developed Namisol, a preparation of dronabinol formulated with an emulsifier in oral tablets. The company is currently preparing phase II clinical trials of Namisol in neuropathic pain, multiple sclerosis and Alzheimer's disease. Nabilone is marketed under the name Cesamet, which is a registered trademark of Valeant Pharmaceuticals International. Cesamet comes in the form of crystalline powder capsules, containing 1 mg nabilone, and is available in the UK, Canada, and in some European countries.

A unique cannabinoid preparation that is currently in clinical use is GW Pharmaceutical's cannabis-plant derived medicine, Sativex™ (GW-1000). This is a natural preparation that standardises THC with cannabidiol in a fixed ratio (1:1.08) and is administered using sublingual sprays or tablets, and oromucosal or oropharyngeal sprays (Smith, 2004). Cannabidiol is thought to have a quite different mechanism of action to THC, and so Sativex is a more complex drug than the pure form of THC or THC analogues. In theory, cannabidiol should work in synergy with THC to increase some of its beneficial effects, and reduce some of its adverse effects. By using a whole plant extract, GW Pharmaceuticals hope to retain some of the putative properties of whole cannabis, as opposed to isolated THC, but

in concentrations that are below that which are thought to cause the major detrimental effects of cannabis. By combining THC and cannabidiol in a fixed ratio, and processing the whole plant extract such that concentrations are precisely specified, Sativex can be administered as a metered and recordable dose, unlike cannabis. Sativex has been approved for use in Canada as a treatment to help reduce pain and tremor in patients with multiple sclerosis, and has been approved for off label use in other countries. Similarly, Cannador® consists of capsules containing a standardized cannabis extract, with a 2:1 ratio of THC to cannabidiol. The cannabis has been grown in Switzerland and processed in Germany, organised by the Institute for Clinical Research (IKF) in Berlin. While Cannador has been used in clinical testing for a number of indications, it has not been licensed for therapeutic use.

While many cannabinoid formulations are not specifically licensed for pain conditions, managing pain is a very useful side effect of cannabinoids used in palliative care in conditions such as HIV/AIDS and multiple sclerosis, and for the adverse effects of chemotherapy. HIV infection is a well known cause of periperheral neuropathies, while multiple sclerosis is a demyelinating neurodegenerative disorder that can also cause serious neuropathic path. Some chemotherapeutics can also cause neuropathies and chronic pain, for example paclitaxel (taxol), a frontline anticancer therapeutic.

3.3 Pharmacokinetics

When smoked, 10 to 25% of the THC content of cannabis leaf is absorbed into the bloodstream (Adams *et al.*, 1996). Via the inhalation route, THC reaches peak levels much faster, and ultimately reaches higher peak plasma concentrations than via oral or even oromucosal administration of THC. In one study, smoking cannabis resulted in peak plasma concentrations of THC more than 10 times greater than an equivalent dose of THC given by oromucosal spray, and peak plasma concentrations were reached within 9 minutes, compared to 180 minutes (Robson, 2005). The high peak plasma concentrations of THC that are achieved very rapidly by smoking cannabis may help explain why some users claim that the medical benefits of smoked cannabis are greater than for other THC preparations (Medicines and Healthcare products Regulatory Agency, 2007). However, the "peak and trough" pharmacokinetics of smoked cannabis means that users experience significantly greater psychoactivity than when using Sativex, where gradual dose titration to steady state plasma concentrations is possible.

Via the oral route, cannabinoids are absorbed much more slowly than via the inhalation route, yet tend to have a longer duration of action. Nabilone and dronabinol are both highly lipophilic compounds, with similar pharmacokinetic profiles when delivered orally. While nabilone and dronabinol have a similar time to onset of action (60 – 90 min and 30 – 60 min, respectively) and peak plasma concentration (2 hours and 2 - 4 hours, respectively), nabilone has a longer duration of action (8 - 12 hours versus 4 – 6 hours, respectively), allowing less frequent dosing. A typical dosing regimen for nabilone in the treatment of chemotherapy-induced nausea and vomiting is 1-2 mg taken 1 to 3 hours prior to chemotherapy and 2 times a day for up to 2 days afterward. For dronabinol, 5 mg may be given 1 to 3 hours before chemotherapy, and every 2 to 4 hours afterwards for a total of 4 to 6 doses each day.

Because cannabinoids are highly lipophilic and pass easily through biological membranes, they can be administered using sublingual sprays or tablets, and oropharyngeal or

oromucosal sprays, as Sativex is. This avoids both first pass metabolism that occurs in oral administration, and the problems associated with smoking and pulmonary administration, while retaining rapid uptake into the blood stream and dispersal around the body and the nervous system that is characteristic of cannabis.

Dronabinol (THC) is primarily metabolized by the cytochrome P450 (CYP450) 2C9 enzyme into 11-hydroxy-THC, and to a lesser degree by CYP3A4 into 7- or 8-hydroxy metabolites (Watanabe et al., 2007). The metabolite 11-hydroxy-THC is pharmacologically active, and polymorphisms of CYP2C9 have been shown to be related to differences in THC response profiles (Sachse-Seeboth et al., 2009), which is an important therapeutic consideration. The exact mechanisms of nabilone metabolism are not known, however it undergoes rapid metabolism to several metabolites including isomeric carbinols (Rubin et al., 1977), and given the long duration of action relative to its rapid metabolism, it has been postulated that some metabolites of nabilone are pharmacologically active.

4. Clinical evidence

4.1 Self-medication with cannabis

Despite the difficulties of obtaining reliable data, epidemiological studies have found that people with conditions varying from chronic pain, multiple sclerosis (MS), and spinal cord injury sometimes self-medicate with cannabis (Ware et al., 2002). Because cannabis is a restricted drug, for which both possession and supply are illegal in most countries, these surveys have often tended to come from Canada, where the practice of self-medication with cannabis is most openly tolerated (Ogborne *et al.*, 2000a; Ogborne *et al.*, 2000b), although some data is available from the US, UK, and continental Europe.

In Canadian studies of people with chronic pain, up to 38% of the subjects used cannabis daily , with 58% of those people using cannabis more than once a day (Ware et al., 2003). Consumption of cannabis was between 1 and 5 grams a day, which represents up to approximately 65mg THC per day (Lynch et al., 2006). In the UK, 25% of sufferers of chronic pain surveyed had self-medicated with cannabis (Ware et al., 2005). Woolridge and colleagues (Woolridge et al., 2005) found that among 523 HIV-positive patients, almost 27% reported (in an anonymous questionnaire) that they used cannabis to help with HIV associated pain, and most users reported that they experienced improvements in muscle pain (94%) and neuropathic pain (90%).

Some surveys have suggested that large numbers of patients with MS might self-medicate with cannabis (Clark *et al.*, 2004; Ware *et al.*, 2005). In one survey in the UK, 75 patients with MS were questioned, of which 49 experienced chronic pain. Of these patients, 83.7% had tried cannabis to help treat their condition, and 75.6% reported that it provided some relief for their pain (Chong et al., 2006). In an earlier survey that targeted patients with MS that self-medicated with cannabis, some 95% of respondents reported that cannabis improved chronic pain to their extremities, spasticity, and some other symptoms such as bladder and bowel dysfunction (Consroe et al., 1997).

The use of cannabis to treat HIV related symptoms was assessed by Woolridge and colleagues (Woolridge et al., 2005), who surveyed the use of cannabis in HIV-positive individuals attending a large clinic with an anonymous cross-sectional questionnaire. Of

those that responded (n=523) 27% reported that they self-medicated with cannabis. Cannabis was reported by the patients to improve appetite (97%), muscle pain (94%), nausea (93%), nerve pain (90%), and paresthesia (85%), but also anxiety (93%) and depression (86%). However, the survey also found that 47% of the cannabis users reported some degree of memory loss.

People with spinal cord injury are another group where self-medication with cannabis is often reported. At the 1998 International Cannabinoid Research Society meeting Consroe and colleagues (Consroe et al., 1998) reported the results of a survey of 190 people with spinal cord injury who belonged to the Alliance for Cannabis Therapeutics of the US. Of the 106 valid respondents, 70% used cannabis along with other medications, and 82% reported that their symptoms became worse when they stopped using cannabis. Improvements were reported for muscle spasms, bladder control, muscle and phantom pains, headache, parathesia, and even paralysis. In a more recent survey of patients with spinal cord injury in the US (Cardenas *et al.*, 2006), 117 patients were questioned about current and past use of treatments. One in seven patients reported having tried an alternative treatment, with cannabis being the most frequently cited. Cannabis was reported to reduce chronic pain by this group by 6.6 points on an 11 point scale, greater than the degree of relief provided by their opioid medications (6.3 points).

In surveys where medicinal cannabis users were targeted, their reasons for use varied considerably, although pain related conditions often appeared high on the list. Schnelle and colleagues reported the results of an anonymous survey of medicinal cannabis users in Germany, Austria and Switzerland (Schnelle et al., 1999). Out of 128 patients that could be included, 12% used medicinal cannabis for depression, 10.8% for MS, 9% HIV-infection, 6.6% migraine, 6% asthma, 5.4% back pain (and 2.4% disk prolapse), 2.4% spinal cord injury, 3% glaucoma, 3.6% spasticity, and 3% nausea. Other conditions included hepatitis C, sleeping disorders, epilepsy, headache, and alcoholism. In this survey, 72.2% of the patients reported that their symptoms were "much improved" by cannabis. In another study, Swift and colleagues (Swift et al., 2005) published the results of an Australian survey following approval of the trial of medical cannabis by the New South Wales State Government. Anonymous questionnaires from 128 participants revealed self-medication with cannabis for chronic pain (57%), depression (56%), arthritis (35%), nausea (27%) and weight loss (26%). Cannabis was also reported to provide substantial relief for pain, nausea and insomnia (Swift et al., 2005). Overall, Australian medical cannabis users reported considerable relief from their symptoms.

Broad survey data on cannabis use sometimes pool recreational and medicinal users, however, despite differences between patterns and levels of use These studies can therefore tend to record frequency of use rather than amounts and potency, measures that are not precisely relevant to people who are self-medicating. Therefore, informal anecdotal or broad survey data is an unreliable guide as to the typical amounts of cannabis and equivalent THC dosages used by people who are self-medicating.

4.2 Clinical case reports

Between surveys and randomized clinical trials are clinical case reports. These are often suggestive of a therapeutic effect, but with low N numbers and often lacking placebo

controls, are hard to interpret, and sometimes contradict the results of non-clinical experiments. For example, cannabis has been reported by some doctors to reduce pendular nystagmus (Schon *et al.*, 1999; Dell'Osso, 2000), but careful experimentation with more sensitive instruments appears to show that cannabis has little or no effect on the functioning of the vestibular system in humans (Spector, 1973).

Some of the best case studies are controlled experiments, albeit with an N of 1, and include controls consisting of placebos or other drugs. For example, in a study of patient with chronic pain from Mediterranean fever, it was found that the patient significantly increased morphine administration when during periods in the study when he was given a placebo instead of 50 mg THC (Holdcroft et al., 1997). In another study, a single patient with spinal cord injury was treated with either oral THC (5 mg), codeine (50 mg), or a placebo in a double blind trial (Maurer et al., 1990). The study found that THC had a similar analgesic effect to codeine when compared with the placebo, and furthermore that THC reduced spasticity.

Although small clinical case studies and experiments continue to appear in the literature, and although they are of enormous value in indicating valuable directions for more intensive clinical research, the evidence base for the use of cannabinoid therapeutics is rapidly becoming dominated by larger scale clinical trials. For good compilations of clinical observation and anecdote, together with the best clinical trial data of the time and expert interpretation, three publications all released in 1997 by the British Medical Association (BMA) (BMA, 1997), the US National Institutes of Health (NIH) (Bethesda, 1997), and the American Medical Association (AMA) (*Report of the Council on Scientific Affairs to AMA House of Delegates on Medical Marijuana.*, 1997) are authoritative. Additional compilations of patient and doctor testimony can be found in Iversen (Iversen, 2000).

4.3 Randomized clinical trials

4.3.1 Acute pain

Campbell et al. (Campbell et al., 2001) reviewed controlled clinical trials, and found that in two trials of acute pain, THC or analogues at tolerable doses were no more effective than codeine, despite increased psychoactivity . Similarly, smoked cannabis was shown to be ineffective in models of experimental acute pain in healthy volunteers, and actually appeared to increase pain sensitivity at higher doses (Hill *et al.*, 1974; Wallace *et al.*, 2007). While this suggests that cannabinoids have minimal efficacy in treating acute nociceptive pain, research in to the use of cannabinoids as adjuvants to opiates for acute pain continues (Greenwald *et al.*, 2000; Buggy *et al.*, 2003; Naef *et al.*, 2003). At least one clinical study has found that THC interacts with morphine to reduce the emotional component of pain (Roberts et al., 2006). Adjuvant therapy would be an attractive therapeutic option due to the adverse effects of opioids when administered at therapeutic doses. Morphine and other opioids cause a number of unwanted and often dose limiting effects, such as constipation, respiratory depression, drowsiness, lack of awareness, and even opioid induced hyperalgesia.

4.3.2 Neuropathic pain

Ashton and Milligan (Ashton *et al.*, 2008) reviewed clinical trials on cannabinoid treatment of neuropathic pain, and found that 15 studies from a total of 18 demonstrated a moderate beneficial effect from cannabinoid treatment.

Wade et al. (Wade et al., 2003) tested whether cannabis extracts (THC, cannabidiol, or Sativex) could treat neurogenic pain and spasm that were intractable to conventional treatment. Pain relief from the drugs was significantly greater than from the placebo. Notcutt et al. (Notcutt et al., 2004) reported that the same three drugs were effective treatments for neuropathic pain, with a side effect profile similar to that for other psychoactive drugs for chronic pain. Berman et al. (Berman et al., 2004) found that Sativex and GW-2000-02 (a cannabis extract containing mostly THC; GW Pharmaceuticals) reduced pain from brachial plexus avulsion for patients with pain refractory to other analgesics, while Sativex has shown further promise in treating allodynia in neuropathic pain syndromes of varying origin (Nurmikko et al., 2007). Pinsger et al. (Pinsger et al., 2006), and Berlach et al. (Berlach et al., 2006) have both tested whether nabilone can control chronic pain, and found a statistically significant decrease in pain, with side effects generally mild. Ajulemic acid, a synthetic analogue of an active metabolite of THC, was found to reduce neuropathic pain in a study by Kaarst et al. (Karst et al., 2003). The results of the study were further extended by Salim et al. (Salim et al., 2005), who calculated that for a clinically relevant 30% reduction in pain, NNT values were 2.14 and 5.29 in two subgroups of patients.

Clinical trials of cannabinoids in multiple sclerosis induced pain are similarly positive. Svendsen et al. (Svendsen et al., 2004) found that pain was reduced by dronabinol in patients with multiple sclerosis related central pain. Nabilone was tested in multiple sclerosis by Wissel et al. (Wissel et al., 2006) who found that pain was reduced by nabilone, but not placebo. A trial of Sativex for the treatment of patients with multiple sclerosis and refractory neuropathic pain by Rog et al. (Rog et al., 2005), found that Sativex relieved pain and was mostly well tolerated. Wade et al. (Wade et al., 2006), in a follow up open-label study to the earlier placebo-controlled trial (Wade et al., 2004) found that mean pain scores were reduced over a 6 week placebo-controlled trial period and then were reduced in the open label study to 40-50% of the baseline scores by weeks 10-26. In the UK, the "Cannabinoids in Multiple Sclerosis (CAMS)" trial compared cannabis extract (Cannador) and dronabinol with placebo (Zajicek et al., 2003). Pain was significantly improved by treatment with either cannabinoid preparation over placebo. Following the main study there was a follow-up double-blinded trial for 12 months (Zajicek et al., 2005), and pain was again relieved to a greater degree in cannabinoid groups over the placebo group.

Two other pain syndromes, HIV-related pain and fibromyalgia deserve special note. Smoked cannabis was found to significantly reduce HIV-induced neuropathic pain by (Abrams et al., 2007), and fibromyalgia-related pain has now been found to be significantly reduced by THC analogues in a number of clinical studies (Schley *et al.*, 2006; Wood *et al.*, 2007; Skrabek *et al.*, 2008).

Clinical evidence for the efficacy of cannabinoids in the treatment of neuropathic pain has not all been positive, and several trials have reported a lack of efficacy. Two of these trials, by Claremont-Gnamien et al. (Clermont-Gnamien et al., 2002) and Attall et al. (Attal et al., 2004), used oral dronabinol, but lacked placebo-controls. In a well controlled study, another report found that nabilone performed poorly compared with dihydrocodeine in treating neuropathic pain of varying origins (Frank et al., 2008). Despite the efficacy of Sativex in treating painful neuropathies (Nurmikko et al., 2007), a recent study in patients suffering painful diabetic neuropathy has been disappointing, with Sativex having no greater effect at relieving pain than placebo (Selvarajah et al., 2010). Similarly , Wade et al. (Wade et al.,

2004) failed to find a beneficial effect on multiple sclerosis induced pain using Sativex. In this instance, Iskedjian et al. (Iskedjian et al., 2007) noted that the placebo effect was unusually large, and patients had unrestricted access to other analgesics. Arguably if Sativex was actually effective in the trial, patients receiving the placebo would initially experience more pain, but then take more of the other analgesics, increasing the apparent pain reduction in the placebo group. This is feasible, as in one case report, a patient with chronic pain increased use of morphine during periods when he was given a placebo instead of THC (Holdcroft et al., 1997).

4.3.3 Secondary outcomes

Sleep is also an essential aspect of quality of life, and patients with chronic pain often have difficulty sleeping. Sleep disturbance is itself disturbing and unpleasant, and lack of sleep contributes to fatigue during waking hours. Insomnia is generally treated with central nervous system depressants, which have a number of problems with long term use, including the development of tolerance and dependence, rebound anxiety and insomnia (as well as more severe withdrawal effects), and problems with cognition. Cannabinoids have soporific effects, and the possibility that cannabinoids can help improve sleep when given to patients with chronic pain has been the subject of clinical trials, generally as a secondary outcome measure. In particular, Russo and colleagues (Russo et al., 2007) reviewed the effects of either Sativex in nine clinical trials where sleep disturbance, duration and/or quality was recorded as a secondary outcome measure. The primary outcome measures of these trials were effects on pain, symptoms of multiple sclerosis, and symptoms of arthritis. Seven out of nine trials found that sleep was improved in patients receiving Sativex compared to patients receiving placebo.

4.4 Assessing the evidence

In 1997 the British Medical Association reviewed 8 clinical studies (BMA, 1997) and concluded that cannabinoids have a role as adjuvant analgesics for pain conditions refractory to standard drugs. Also in 1997, similar conclusions were made in reports by the American Medical Association (*Report of the Council on Scientific Affairs to AMA House of Delegates on Medical Marijuana.*, 1997) and the US National Institutes of Health (Bethesda, 1997). Despite this, it is clear to see that the evidence from clinical trials is not consistent, with some but not all trials showing a moderate effect on neuropathic pain from cannabinoid treatment.

The inconsistency of the evidence may be partly due to the inconsistency of the quality of the randomized clinical trials. The risk of unblinding of subjects to treatment has been high in a number of trials; some subjects had prior exposure to cannabis or even cannabinoid drugs in open phases of the trials. Another possible explanation for the inconsistency of evidence could be the heterogeneity of pain syndromes and outcome measures across trials. Much of the evidence for antinociceptive effects in neuropathic pain comes from studies primarily aimed at assessing spasticity in multiple sclerosis, or neuropathic pain of varying origin and severity. In conditions with severe neuropathies, cannabinoids at tolerable doses may be less efficacious. This is illustrated by the disparity between the positive results of Nurmikko et al. (Nurmikko et al., 2007), who report Sativex was efficacious in the treatment of neuropathic pain of different origins, and those of Selvarajah et al., (Selvarajah et al.,

2010), who report no effect of Sativex on painful poly-neuropathy. This issue is discussed in a major recent systematic review of drug treatment for neuropathic pain (Finnerup et al., 2010). In it, Finnerup et al. concluded that cannabinoids have a small effect on central pain in multiple sclerosis, mixed neuropathic pain and in peripheral neuropathic pain, but not in painful poly-neuropathy.

A meta-analysis published in 2007 (Iskedjian et al., 2007) reported that cannabinoids are useful for neuropathic pain. Iskedjian et al. (Iskedjian et al., 2007) analysed data from 6 published studies and additional unpublished data from GW Pharmaceuticals. Sativex decreased pain by 1.7 +/- 0.7 points ($p = 0.018$) on an 11-point scale; cannabidiol by 1.5 +/- 0.7 points ($p = 0.044$); dronabinol by 1.5 +/- 0.6 points ($p = 0.013$). Pooling the 3 drugs together, pain reduction was 1.6 +/- 0.4 points ($p < 0.001$) for the cannabinoid group, in contrast to 0.8 +/- 0.4 points ($p = 0.023$) for the placebo. Average baseline scores in the trials were around 50-70% of the maximum possible pain, thus a cannabinoid-induced 1.6 point reduction on a 11-point scale would be equate to an approximately 24% reduction in pain. An important consideration in analysing this clinical data is that many trials have studied patients with pain refractory to conventional treatment, and concomitant analgesia is the norm, thus some part of the analgesia provided by the cannabinoids may be masked. In addition, most trials only tested for pain reduction for a short time; Isdekjian et al. (Iskedjian et al., 2007) found that pain reduction was doubled in subjects receiving a cannabis-based medicinal extract (CBME) at 6-10 weeks compared with earlier times, an approximate halving of baseline pain scores. It was further suggested that the patients in the drug group who showed improvement for pain could be "cannabinoid responders" who have greater than the average pain relief.

5. Safety and tolerability

5.1 Adverse events

In clinical trials using cannabinoids, adverse side effects are dose dependent, and appear to vary in intensity from trial to trial, and between individuals within trials. Possible side effects include euphoria, dysphoria, anxiety, depersonalisation, sedation and drowsiness, distorted perception, mental clouding, memory impairment, impairment on cognitively demanding tasks, fragmentation of thoughts, and even hallucinations. Cannabinoids also stimulate appetite, and in some contexts this might possibly be considered an undesired effect; though it is an effect that is actively sought when cannabinoids are used to stimulate weight gain in patients suffering from wasting after HIV infection or chemotherapy. Acute cannabis toxicity can cause psychotic episodes involving delusions and paranoia. With respect to motor function, cannabis can cause hypermotility (increased motor activity, movement) followed by lethargy, lack of coordination or ataxia, muscle twitches, tremors and weakness, and problems speaking (dysarthia). Pregnant women should avoid cannabinoids, as this been linked to the impairment of fetal development (Hurd *et al.*, 2005; Huizink *et al.*, 2006), even though the evidence for this is inconsistent (Chiriboga, 2003).

Most clinical trials discussed earlier also contain data on adverse effects. These are mostly minor, and virtually all the trials describe the drug as "well tolerated". The most common side effects reported in the trials are drowsiness, ataxia, euphoria and dizziness. At higher doses, dissociation and distorted perception are infrequently reported. For example, in the

trials carried out by Berman et al. (Berman et al., 2004) and Rog et al. (Rog et al., 2005), approximately 25 mg of THC was used, and adverse effects were mild to moderate, and usually spontaneously resolved. In both trials the most common side effects were dizziness and drowsiness. In the Rog et al. (Rog et al., 2005) trial, 53% of patients experienced at least one episode of dizziness, 1 out of 34 patients experienced drowsiness ("somnolence") and 1 out of 34 experienced dissociation and ataxia ("feeling drunk"). It is important to note that this trial (which is typical) recorded at least one minor adverse event for 88.2% of patients on the drug, but to put this in context, the figure is 68.8% for patients taking the placebo.

As neuropathic pain is a condition requiring long term treatment, it is important to assess the adverse effects of any treatment over an appropriate time course. Wade et al. (Wade et al., 2006) and Zajicek et al. (Zajicek et al., 2005) both reported on the long term effects of THC medication in pain conditions. Wade et al. (Wade et al., 2006) extended a placebo controlled acute trial in multiple sclerosis patients, and investigated long term Sativex use in an open label trial. They noted that adverse effects were mild in most cases, and the few serious events recorded (seizure, gastroenteritis, pneumonia) could not be definitively linked to Sativex use, as patients were taking other medications, and multiple sclerosis in itself is a risk factor for some of the recorded events. Similarly, Zajicek et al. (Zajicek et al., 2005) extended a placebo controlled trial of dronabinol and cannabis extract (Cannador) in multiple sclerosis patients, and recorded adverse events for a year. Unlike the Wade et al. follow up, the design of the study allowed comparison of cannabinoid treatment with an inactive placebo. While minor and serious adverse events were reported in the cannabinoid groups, incidence rates were comparable with placebo (Zajicek et al., 2005). Overall both studies conclude that in general, adverse effects were mild, and long term cannabinoid treatment was well tolerated.

5.2 Tolerance and dependence

In studies dealing with self medication with cannabis, it is difficult to accurately calculate equivalent doses of THC, as frequency, amount, and potency of smoked cannabis leaf are highly variable between users. A recent study with 30 subjects in Canada found that people who used cannabis to treat themselves for chronic pain used between 1 and 5 grams of cannabis a day, with an average of 2.5 grams/day (Lynch et al., 2006). The THC content in cannabis cigarettes usually ranges between 1.5 to 3.7%, so smoking 2.5g per day translates into a daily intake of 38 to 93 mg of THC. As only 10 to 25% of the THC in smoked cannabis leaf will be absorbed into the bloodstream (Adams *et al.*, 1996), this equates to 3.8 to 23 mg of THC per day. The other systematic source of data on amounts of THC that will be sought by people seeking relief from chronic pain comes from clinical trials where the patients are allowed to "self-titrate". This is where the patient has *ad libitum* access to the drug (within an upper limit), and takes the drug as required. In this way, the patient finds a balance between the desired and undesired effects to fit their individual needs. In these self-titrating trials, 25 mg of THC was a typical amount of the drug that was taken during a day. Therefore, there appears to be a reasonable correlation between the amounts of THC that people seek from self-medication with cannabis, and from purified extracts in clinical trials.

People who self-titrate, or self-medicate for THC may raise the dose that they seek over time, because they can become tolerant to the analgesic effects of THC (Association, 1997; Lichtman *et al.*, 2005), and thus seek higher amounts to relieve their pain. At the same time,

tolerance also occurs to adverse effects, such as drowsiness and sedation. With respect to euphoria and minor adverse effects, moderate and heavy users of cannabis do develop tolerance (i.e., a decreased response to the drug) (Lichtman *et al.*, 2005). In one study, heavy users smoked an average 5.7 grams of cannabis a day, and showed a progressive decline in ratings of intoxication (Babor et al., 1975).

Cannabis dependence is a recognised syndrome under DSM-IV criteria, and has been the subject of a number of epidemiological studies (e.g., (Fergusson *et al.*, 2003; Boden *et al.*, 2006)). The official advice seems to indicate that cannabis dependence is not prevalent. The UM MRHA 2007 report on Sativex states that only 1% of cannabis users develop dependence on the drug. The prescription data sheets for Cesamet and Marinol state that in clinical trials of these formulations in patient populations, patients experienced no withdrawal symptoms, despite a 5 month trial in the case of Marinol. Both data sheets, however, point to an abstinence syndrome in healthy volunteers after the cessation of large daily doses of THC (200 mg), administered over 12 – 16 days. Withdrawal symptoms included some distress, sleep disturbances and autonomic hyperactivity, lasting for 48 hours after drug cessation.

6. Future drug development

One of the limiting factors for the widespread clinical use of cannabinoids is adverse psychoactivity. As discussed earlier, this is caused exclusively by activation of CB1 receptors in the central nervous system. One important aim of research into cannabinoid receptors as therapeutic targets is to obtain ligands with clinically useful effects, but without (or at least minimizing) the psychoactive unwanted effects. The chronic pain relieving properties are thought to be mediated via activation of not only central CB1 receptors, but also spinal and peripheral CB1 and CB2 receptors. Recent cannabinoid drug development has attempted to exploit the apparent redundancy of the cannabinoid system in pain, developing ligands selective for non-psychoactive or peripheral cannabinoid receptors.

Because of the distinct distributions and physiological functions of CB1 and CB2, there has been intensive research into developing ligands specific for a particular receptor, particularly the "non-psychoactive" CB2 receptor. HU-308 is a highly selective bicyclic CB2-agonist, related to WIN55,212-2 and JWH-133, with a 440-fold selectivity for CB2 over CB1 (Hanus et al., 1999). At the time of writing, HU-308 has restricted availability, and is being intensively studied by several research groups for its potential therapeutic potential. Another highly selective CB2 agonist, GW405833, has been synthesised (Valenzano et al., 2005), and is also a derivative of WIN55,212-2. Crucially, although this compound has only 80-fold selectivity for the CB2 receptor over the CB1 receptor in rats, it has a 1200-fold selectivity for CB2 over CB1 in humans. GW405833 is a partial agonist at CB2 (Kearn et al., 1999). Preclinical research into these compounds has been promising, although clinical translation has been less so. GlaxoSmithKline tested GW842166, a potent CB2 agonist, and found it to be highly efficacious in an animal model of inflammatory pain. In the clinic, however, this compound had no effect on acute dental pain compared to placebo in a paradigm where 800 mg ibuprofen was efficacious (Ostenfeld et al., 2011). This said, it must be questioned why a condition of acute pain was chosen for clinical testing in this instance, as cannabinoids have typically been more efficacious in chronic pain conditions.

Alternatively, the selective targeting of peripheral cannabinoid receptors would also circumvent unfavourable psychoactivity. AstraZeneca have been conducting preclinical and

clinical trials with several peripherally restricted cannabinoid agonists with mixed results. Preclinical trials with AZ11713908 (Yu et al., 2010) and AZD1940 (Groblewski *et al.*, 2010b) indicated antinociceptive efficacy in animal models of inflammatory and neuropathic pain, and minimal CNS penetration. In clinical trials, however, AZD1940 reportedly had no effect on acute dental pain, or chronic back pain (Groblewski *et al.*, 2010a).

7. Conclusions

Cannabis is widely used by people suffering from neuropathic pain, with many users reporting pain relieving effects. In more quantitative analyses, cannabinoids appear to have a moderate efficacy in the treatment of chronic and neuropathic pain of varying origin, with adverse effects and dependence risk minimal when compared with traditional analgesics, especially opioids. Despite a lack of efficacy in every neuropathic condition, and dose limiting adverse effects of these compounds, there appears to be a large body of evidence supporting a continued role of cannabinoids as analgesics in some instances, especially in patients refractory to current treatments. The development of more efficacious and well tolerated drugs in this class will enable a more widespread application these pharmacotherapeutics in neuropathic pain.

8. References

Abrams, DI, Jay, CA, Shade, SB, Vizoso, H, Reda, H, Press, S, Kelly, ME, Rowbotham, MC, Petersen, KL. (2007). Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology,* Vol. 68, No. 7, pp. (515-521)

Adams, IB, Martin, BR. (1996). Cannabis: pharmacology and toxicology in animals and humans. *Addiction,* Vol. 91, No. 11, pp. (1585-1614)

Agarwal, N, Pacher, P, Tegeder, I, Amaya, F, Constantin, CE, Brenner, GJ, Rubino, T, Michalski, CW, Marsicano, G, Monory, K, Mackie, K, Marian, C, Batkai, S, Parolaro, D, Fischer, MJ, Reeh, P, Kunos, G, Kress, M, Lutz, B, Woolf, CJ, Kuner, R. (2007). Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. *Nat Neurosci,* Vol. 10, No. 7, pp. (870-879)

Ashton, JC, Milligan, ED. (2008). Cannabinoids for the treatment of neuropathic pain: clinical evidence. *Curr Opin Investig Drugs,* Vol. 9, No. 1, pp. (65-75)

Association, BM (1997) *Therapeutic uses of Cannabis*. Harwood Academic Publishers, Amsterdam.

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,* Vol. 8, No. 2, pp. (173-177)

Babor, TF, Mendelson, JH, Greenberg, I, Kuehnle, JC. (1975). Marijuana consumption and tolerance to physiological and subjective effects. *Arch Gen Psychiatry,* Vol. 32, No. 12, pp. (1548-1552)

Benito, C, Nunez, E, Tolon, RM, Carrier, EJ, Rabano, A, Hillard, CJ, Romero, J. (2003). Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains. *J Neurosci,* Vol. 23, No. 35, pp. (11136-11141)

Berlach, DM, Shir, Y, Ware, MA. (2006). Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. *Pain Med,* Vol. 7, No. 1, pp. (25-29)

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,* Vol. 112, No. 3, pp. (299-306)

Bethesda, MD (1997) *Report on the Medical Uses of Marijuana.*: National Institutes of Health.

BMA (1997) *Therapeutic uses of cannabis*. Harwood Academic Publishers: Amsterdam.

Boden, JM, Fergusson, DM, Horwood, LJ. (2006). Illicit drug use and dependence in a New Zealand birth cohort. *Aust N Z J Psychiatry,* Vol. 40, No. 2, pp. (156-163)

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,* Vol. 106, No. 1-2, pp. (169-172)

Burns, TL, Ineck, JR. (2006). Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. *Ann Pharmacother,* Vol. 40, No. 2, pp. (251-260)

Cabral, G, Marciano-Cabral, F. (2005). Cannabinoid receptors in microglia of the central nervous system: immune functional relevance. *J Leukoc Biol.,* Vol. 78, No. 6, pp. (1192-1197)

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,* Vol. 323, No. 7303, pp. (13-16)

Cardenas, DD, Jensen, MP. (2006). Treatments for chronic pain with spinal cord injury: A survey study. *J Spinal Cord Med.,* Vol. 29, No. 2, pp. (109-117)

Chiriboga, CA. (2003). Fetal alcohol and drug effects. *Neurologist,* Vol. 9, No. 6, pp. (267-279)

Chong, MS, Wolff, K, Wise, K, Tanton, C, Winstock, A, Silber, E. (2006). Cannabis use in patients with multiple sclerosis. *Mult Scler,* Vol. 12, No. 5, pp. (646-651)

Clark, AJ, Ware, MA, Yazer, E, Murray, TJ, Lynch, ME. (2004). Patterns of cannabis use among patients with multiple sclerosis. *Neurology,* Vol. 62, No. 11, pp. (2098-2100)

Clarke, RC, Watson, DP (2002) Botany of Natural Cannabis Medicines. In: *Cannabis and Cannabinoids: Pharmacology and Toxicology and Therapeutic Potential*, Grotenhermen, MD, Russo, E (eds), pp 3-13. New York: The Hawthorn Integrative Healing Press.

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]. *Presse Med,* Vol. 31, No. 39 Pt 1, pp. (1840-1845)

Compton, DR, Johnson, MR, Melvin, LS, Martin, BR. (1992). Pharmacological profile of a series of bicyclic cannabinoid analogs: classification as cannabimimetic agents. *J Pharmacol Exp Ther.,* Vol. 260, No. 1, pp. (201-209)

Consroe, P, Musty, R, Rein, J, Tillery, W, Pertwee, R. (1997). The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol.,* Vol. 38, No. pp. (44-48.)

Consroe, P, Tillery, W, Rein, J, Musty, RE. (1998). Reported marijuana effects in patients with spinal cord injury., *International Cannabinoid Research Society, Symposium on Cannabinoids,* Burlington, Vermont.,

Cravatt, BF, Giang, DK, Mayfield, SP, Boger, DL, Lerner, RA, Gilula, NB. (1996). Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. *Nature.,* Vol. 384, No. 6604, pp. (83-87)

Cronin, CM, Sallan, SE, Gelber, R, Lucas, VS, Laszlo, J. (1981). Antiemetic effect of intramuscular levonantradol in patients receiving anticancer chemotherapy. *J Clin Pharmacol,* Vol. 21, No. 8-9 Suppl, pp. (43S-50S)

Dell'Osso, LF. (2000). Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. *Neurology,* Vol. 54, No. 11, pp. (2190-2191)

Devane, WA, Dysarz, FA, 3rd, Johnson, MR, Melvin, LS, Howlett, AC. (1988). Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol.,* Vol. 34, No. 5, pp. (605-613.)

Devane, WA, Hanus, L, Breuer, A, Pertwee, RG, Stevenson, LA, Griffin, G, Gibson, D, Mandelbaum, A, Etinger, A, Mechoulam, R. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science.,* Vol. 258, No. 5090, pp. (1946-1949.)

Di Marzo, V. (2006a). A brief history of cannabinoid and endocannabinoid pharmacology as inspired by the work of British scientists. *Trends Pharmacol Sci.,* Vol. 27, No. 3, pp. (134-140)

Di Marzo, V. (2006b). A brief history of cannabinoid and endocannabinoid pharmacology as inspired by the work of British scientists. *Trends Pharmacol Sci,* Vol. 27, No. 3, pp. (134-140)

Dinh, TP, Carpenter, D, Leslie, FM, Freund, TF, Katona, I, Sensi, SL, Kathuria, S, Piomelli, D. (2002). Brain monoglyceride lipase participating in endocannabinoid inactivation. *Proc Natl Acad Sci U S A.,* Vol. 99, No. 16, pp. (10819-10824)

Elphick, MR, Egertova, M. (2001). The neurobiology and evolution of cannabinoid signalling. *Philos Trans R Soc Lond B Biol Sci.,* Vol. 356, No. 1407, pp. (381-408.)

Fergusson, DM, Horwood, LJ, Lynskey, MT, Madden, PA. (2003). Early reactions to cannabis predict later dependence. *Arch Gen Psychiatry,* Vol. 60, No. 10, pp. (1033-1039)

Finnerup, NB, Sindrup, SH, Jensen, TS. (2010). The evidence for pharmacological treatment of neuropathic pain. *Pain,* Vol. 150, No. 3, pp. (573-581)

Frank, B, Serpell, MG, Hughes, J, Matthews, JN, Kapur, D. (2008). Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *Bmj,* Vol. 336, No. 7637, pp. (199-201)

Frankhauser, M (2002) History of Cannabis in Western Medicine. In: *Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential.*, Grotenhermen, F, Russo, E (eds). New York: The Haworth Integrative Healing Press.

Galiegue, S, Mary, S, Marchand, J, Dussossoy, D, Carriere, D, Carayon, P, Bouaboula, M, Shire, D, Le Fur, G, Casellas, P. (1995). Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Eur J Biochem.,* Vol. 232, No. 1, pp. (54-61)

Gerard, CM, Mollereau, C, Vassart, G, Parmentier, M. (1991). Molecular cloning of a human cannabinoid receptor which is also expressed in testis. *Biochem J,* Vol. 279, No. 1, pp. (129-134)

Glass, M, Dragunow, M, Faull, RL. (1997). Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience,* Vol. 77, No. 2, pp. (299-318.)

Gong, JP, Onaivi, ES, Ishiguro, H, Liu, QR, Tagliaferro, PA, Brusco, A, Uhl, GR. (2006). Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. *Brain Res,* Vol. 1071, No. 1, pp. (10-23)

Greenwald, MK, Stitzer, ML. (2000). Antinociceptive, subjective and behavioral effects of smoked marijuana in humans. *Drug Alcohol Depend,* Vol. 59, No. 3, pp. (261-275)

Griffin, G, Tao, Q, Abood, ME. (2000). Cloning and pharmacological characterization of the rat CB(2) cannabinoid receptor. *J Pharmacol Exp Ther,* Vol. 292, No. 3, pp. (886-894)

Groblewski, T, Karlsten, R, Segerdhal, M, Kalliomaki, J, Jonzon, B, Bielenstein, M, Cebers, G, Swedberg, M, Annas, A, Christoph, G, Tellefors, P, Stahle, L, Bouw, R, Fagerholm,

U, Berg, A, Butler, S, O'Malley, M, Anstren, G. (2010a). Peripherally-acting CB1-CB2 agonists for pain: do they still hold promise?, *Proceedings of the 20th annual symposium of the international cannabinoid research society,* Lund, Sweden, July 2010.

Groblewski, T, Yu, XH, Laessard, E, St-Onge, S, Yang, H, Panetta, R, Cao, CQ, Swedberg, M, Cebers, G, Nyberg, S, Schou, M, Halldin, C, Gulyas, B, Varnas, K, Walpole, C, Payza, K, Perkins, M, Ducharme, J. (2010b). Pre-clinical pharmacological properties of novel peripherally-acting CB1-CB2 agonists, *Proceedings of the 20th annual symposium of the international cannabinoid research society,* Lund, Sweden, July 2010.

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,* Vol. 96, No. 25, pp. (14228-14233)

Herkenham, M, Lynn, AB, Little, MD, Johnson, MR, Melvin, LS, de Costa, BR, Rice, KC. (1990a). Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A.,* Vol. 87, No. 5, pp. (1932-1936)

Herkenham, M, Lynn, AB, Little, MD, Johnson, MR, Melvin, LS, de Costa, BR, Rice, KC. (1990b). Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A,* Vol. 87, No. 5, pp. (1932-1936)

Hill, SY, Schwin, R, Goodwin, DW, Powell, BJ. (1974). Marihuana and pain. *J Pharmacol Exp Ther,* Vol. 188, No. 2, pp. (415-418)

Holdcroft, A, Smith, M, Jacklin, A, Hodgson, H, Smith, B, Newton, M, Evans, F. (1997). Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia,* Vol. 52, No. 5, pp. (483-486)

Huffman, JW. (2005). CB2 receptor ligands. *Mini Rev Med Chem.,* Vol. 5, No. 7, pp. (641-649.)

Huizink, AC, Mulder, EJ. (2006). Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. *Neurosci Biobehav Rev,* Vol. 30, No. 1, pp. (24-41)

Hurd, YL, Wang, X, Anderson, V, Beck, O, Minkoff, H, Dow-Edwards, D. (2005). Marijuana impairs growth in mid-gestation fetuses. *Neurotoxicol Teratol,* Vol. 27, No. 2, pp. (221-229)

Huskey, A. (2006). Cannabinoids in cancer pain management. *J Pain Palliat Care Pharmacother,* Vol. 20, No. 3, pp. (43-46)

Hutcheon, AW, Palmer, JB, Soukop, M, Cunningham, D, McArdle, C, Welsh, J, Stuart, F, Sangster, G, Kaye, S, Charlton, D, et al. (1983). A randomised multicentre single blind comparison of a cannabinoid anti-emetic (levonantradol) with chlorpromazine in patients receiving their first cytotoxic chemotherapy. *Eur J Cancer Clin Oncol,* Vol. 19, No. 8, pp. (1087-1090)

Iskedjian, M, Bereza, B, Gordon, A, Piwko, C, Einarson, TR. (2007). Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin,* Vol. 23, No. 1, pp. (17-24)

Iversen, L (2000) *The Science of Marijuana.* Oxford University Press: Oxford.

Izzo, AA, Mascolo, N, Capasso, F. (2001). The gastrointestinal pharmacology of cannabinoids. *Curr Opin Pharmacol.,* Vol. 1, No. 6, pp. (597-603)

Jain, AK, Ryan, JR, McMahon, FG, Smith, G. (1981). Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol,* Vol. 21, No. pp. (320S-326S)

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. *JAMA,* Vol. 290, No. 13, pp. (1757-1762)

Kearn, CS, Greenberg, MJ, DiCamelli, R, Kurzawa, K, Hillard, CJ. (1999). Relationships between ligand affinities for the cerebellar cannabinoid receptor CB1 and the induction of GDP/GTP exchange. *J Neurochem.,* Vol. 72, No. 6, pp. (2379-2387)

Lees, G, Dougalis, A. (2004). Differential effects of the sleep-inducing lipid oleamide and cannabinoids on the induction of long-term potentiation in the CA1 neurons of the rat hippocampus in vitro. *Brain Res.,* Vol. 997, No. 1, pp. (1-14)

Lichtman, AH, Martin, BR. (2005). Cannabinoid tolerance and dependence. *Handb Exp Pharmacol,* Vol. No. 168, pp. (691-717)

Lynch, ME, Young, J, Clark, AJ. (2006). A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. *J Pain Symptom Manage,* Vol. 32, No. 5, pp. (497-501)

Machado Rocha, FC, StÉFano, SC, De CÁSsia Haiek, R, Rosa Oliveira, LMQ, Da Silveira, DX. (2008). Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *European Journal of Cancer Care,* Vol. 17, No. 5, pp. (431-443)

Manzanares, J, Julian, MD, Carrascosa, A. (2006). Current Neuropharmacology. *Role of the Cannabinoid System in Pain Control and Therapeutic Implications for the Management of Acute and Chronic Pain Episodes.,* Vol. 4, No. pp. (239-257)

Maurer, M, Henn, V, Dittrich, A, Hofmann, A. (1990). Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *Eur Arch Psychiatry Clin Neurosci,* Vol. 240, No. 1, pp. (1-4)

Mechoulam, R, Ben-Shabat, S, Hanus, L, Ligumsky, M, Kaminski, NE, Schatz, AR, Gopher, A, Almog, S, Martin, BR, Compton, DR, et al. (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol.,* Vol. 50, No. 1, pp. (83-90)

Mechoulam, R, Gaoni, Y. (1965). A Total Synthesis of Dl-Delta-1-Tetrahydrocannabinol, the Active Constituent of Hashish. *J Am Chem Soc.,* Vol. 87, No. pp. (3273-3275)

Medicines and Healthcare products Regulatory Agency, U (2007) *Public Information Report on Sativex Oromucosal Spray: UK/H/961/01/DC.*

Munro, S, Thomas, KL, Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature.,* Vol. 365, No. 6441, pp. (61-65)

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,* Vol. 105, No. 1-2, pp. (79-88)

Njie, YF, Kumar, A, Qiao, Z, Zhong, L, Song, ZH. (2006). Noladin ether acts on trabecular meshwork cannabinoid (CB1) receptors to enhance aqueous humor outflow facility. *Invest Ophthalmol Vis Sci.,* Vol. 47, No. 5, pp. (1999-2005)

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,* Vol. 59, No. 5, pp. (440-452)

Nurmikko, TJ, Serpell, MG, Hoggart, B, Toomey, PJ, Morlion, BJ, Haines, D. (2007). Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain,* Vol. 133, No. 1-3, pp. (210-220)

Ogborne, AC, Smart, RG. (2000a). Cannabis users in the general Canadian population. *Subst Use Misuse,* Vol. 35, No. 3, pp. (301-311)

Ogborne, AC, Smart, RG, Adlaf, EM. (2000b). Self-reported medical use of marijuana: a survey of the general population. *Cmaj,* Vol. 162, No. 12, pp. (1685-1686)

Okamoto, Y, Wang, J, Morishita, J, Ueda, N. (2007). Biosynthetic pathways of the endocannabinoid anandamide. *Chem Biodivers,* Vol. 4, No. 8, pp. (1842-1857)

Onaivi, ES, Ishiguro, H, Gong, JP, Patel, S, Perchuk, A, Meozzi, PA, Myers, L, Mora, Z, Tagliaferro, P, Gardner, E, Brusco, A, Akinshola, BE, Liu, QR, Hope, B, Iwasaki, S, Arinami, T, Teasenfitz, L, Uhl, GR. (2006). Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. *Ann N Y Acad Sci,* Vol. 1074, No. pp. (514-536)

Ostenfeld, T, Price, J, Albanese, M, Bullman, J, Guillard, F, Meyer, I, Leeson, R, Costantin, C, Ziviani, L, Nocini, PF, Milleri, S. (2011). A Randomized, Controlled Study to Investigate the Analgesic Efficacy of Single Doses of the Cannabinoid Receptor-2 Agonist GW842166, Ibuprofen or Placebo in Patients With Acute Pain Following Third Molar Tooth Extraction. *Clin J Pain,* Vol. 27, No. 8, pp. (668-676)

Pacher, P, Batkai, S, Kunos, G. (2006). The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev.,* Vol. 58, No. 3, pp. (389-462.)

Park, B, Gibbons, HM, Mitchell, MD, Glass, M. (2003). Identification of the CB1 cannabinoid receptor and fatty acid amide hydrolase (FAAH) in the human placenta. *Placenta.,* Vol. 24, No. 10, pp. (990-995)

Pertwee, RG. (2001). Cannabinoid receptors and pain. *Prog Neurobiol,* Vol. 63, No. 5, pp. (569-611)

Pinsger, M, Schimetta, W, Volc, D, Hiermann, E, Riederer, F, Polz, W. (2006). [Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain--a randomized controlled trial]. *Wien Klin Wochenschr,* Vol. 118, No. 11-12, pp. (327-335)

Report of the Council on Scientific Affairs to AMA House of Delegates on Medical Marijuana. (1997). American Medical Association.

Rinaldi-Carmona, M, Barth, F, Heaulme, M, Shire, D, Calandra, B, Congy, C, Martinez, S, Maruani, J, Neliat, G, Caput, D, et al. (1994). SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett.,* Vol. 350, No. 2-3, pp. (240-244)

Roberts, JD, Gennings, C, Shih, M. (2006). Synergistic affective analgesic interaction between delta-9-tetrahydrocannabinol and morphine. *Eur J Pharmacol,* Vol. 530, No. 1-2, pp. (54-58)

Robson, P. (2005). Human studies of cannabinoids and medicinal cannabis. *Handb Exp Pharmacol,* Vol. No. 168, pp. (719-756)

Rog, DJ, Nurmikko, TJ, Friede, T, Young, CA. (2005). Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology,* Vol. 65, No. 6, pp. (812-819)

Rubin, A, Lemberger, L, Warrick, P, Crabtree, RE, Sullivan, H, Rowe, H, Obermeyer, BD. (1977). Physiologic disposition of nabilone, a cannabinol derivative, in man. *Clin Pharmacol Ther,* Vol. 22, No. 1, pp. (85-91)

Russo, EB, Guy, GW, Robson, PJ. (2007). Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem Biodivers,* Vol. 4, No. 8, pp. (1729-1743)

Sachse-Seeboth, C, Pfeil, J, Sehrt, D, Meineke, I, Tzvetkov, M, Bruns, E, Poser, W, Vormfelde, SV, Brockmoller, J. (2009). Interindividual variation in the pharmacokinetics of

Delta9-tetrahydrocannabinol as related to genetic polymorphisms in CYP2C9. *Clin Pharmacol Ther,* Vol. 85, No. 3, pp. (273-276)

Salim, K, Schneider, U, Burstein, S, Hoy, L, Karst, M. (2005). Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. *Neuropharmacology,* Vol. 48, No. 8, pp. (1164-1171)

Schley, M, Legler, A, Skopp, G, Schmelz, M, Konrad, C, Rukwied, R. (2006). Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. *Curr Med Res Opin,* Vol. 22, No. 7, pp. (1269-1276)

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]. *Forsch Komplementarmed,* Vol. 6 Suppl 3, No. pp. (28-36)

Schon, F, Hart, PE, Hodgson, TL, Pambakian, AL, Ruprah, M, Williamson, EM, Kennard, C. (1999). Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. *Neurology,* Vol. 53, No. 9, pp. (2209-2210)

Scotter, E, Graham, S, Glass, M (2006) Cannabinoid Receptor Signal Transduction Pathways. In: *Cannabinoids: Structure and Function*, Reggio, P (ed): Humana Press.

Selvarajah, D, Gandhi, R, Emery, CJ, Tesfaye, S. (2010). Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care,* Vol. 33, No. 1, pp. (128-130)

Skrabek, RQ, Galimova, L, Ethans, K, Perry, D. (2008). Nabilone for the treatment of pain in fibromyalgia. *J Pain,* Vol. 9, No. 2, pp. (164-173)

Smith, PF. (2004). GW-1000. GW Pharmaceuticals. *Curr Opin Investig Drugs.,* Vol. 5, No. 7, pp. (748-754)

Spector, M. (1973). Acute vestibular effects of marijuana. *J Clin Pharmacol,* Vol. 13, No. 5, pp. (214-217)

Stambaugh, JE, Jr., McAdams, J, Vreeland, F. (1984). Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapy-induced emesis. *J Clin Pharmacol,* Vol. 24, No. 11-12, pp. (480-485)

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,* Vol. 329, No. 7460, pp. (253)

Swift, W, Gates, P, Dillon, P. (2005). Survey of Australians using cannabis for medical purposes. *Harm Reduct J,* Vol. 2, No. pp. (18)

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.,* Vol. 48, No. 5, pp. (658-672)

van der Stelt, M, Di Marzo, V. (2005). Anandamide as an intracellular messenger regulating ion channel activity. *Prostaglandins Other Lipid Mediat,* Vol. 77, No. 1-4, pp. (111-122)

Van Sickle, MD, Duncan, M, Kingsley, PJ, Mouihate, A, Urbani, P, Mackie, K, Stella, N, Makriyannis, A, Piomelli, D, Davison, JS, Marnett, LJ, Di Marzo, V, Pittman, QJ, Patel, KD, Sharkey, KA. (2005). Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science,* Vol. 310, No. 5746, pp. (329-332)

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,* Vol. 10, No. 4, pp. (434-441)

Wade, DT, Makela, PM, House, H, Bateman, C, Robson, P. (2006). Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler,* Vol. 12, No. 5, pp. (639-645)

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,* Vol. 17, No. 1, pp. (21-29)

Wallace, M, Schulteis, G, Atkinson, JH, Wolfson, T, Lazzaretto, D, Bentley, H, Gouaux, B, Abramson, I. (2007). Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology,* Vol. 107, No. 5, pp. (785-796)

Ware, MA, Adams, H, Guy, GW. (2005). The medicinal use of cannabis in the UK: results of a nationwide survey. *Int J Clin Pract,* Vol. 59, No. 3, pp. (291-295)

Ware, MA, Doyle, CR, Woods, R, Lynch, ME, Clark, AJ. (2003). Cannabis use for chronic non-cancer pain: results of a prospective survey. *Pain,* Vol. 102, No. 1-2, pp. (211-216)

Ware, MA, Gamsa, A, Persson, J, Fitzcharles, MA. (2002). Cannabis for chronic pain: case series and implications for clinicians. *Pain Res Manag,* Vol. 7, No. 2, pp. (95-99)

Watanabe, K, Yamaori, S, Funahashi, T, Kimura, T, Yamamoto, I. (2007). Cytochrome P450 enzymes involved in the metabolism of tetrahydrocannabinols and cannabinol by human hepatic microsomes. *Life Sci,* Vol. 80, No. 15, pp. (1415-1419)

Wissel, J, Haydn, T, Muller, J, Brenneis, C, Berger, T, Poewe, W, Schelosky, LD. (2006). Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. *J Neurol,* Vol. 253, No. 10, pp. (1337-1341)

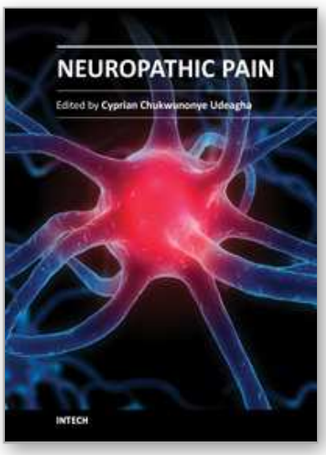
Wood, PB, Holman, AJ, Jones, KD. (2007). Novel pharmacotherapy for fibromyalgia. *Expert Opin Investig Drugs,* Vol. 16, No. 6, pp. (829-841)

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,* Vol. 29, No. 4, pp. (358-367)

Yu, XH, Cao, CQ, Martino, G, Puma, C, Morinville, A, St-Onge, S, Lessard, E, Perkins, MN, Laird, JM. (2010). A peripherally restricted cannabinoid receptor agonist produces robust anti-nociceptive effects in rodent models of inflammatory and neuropathic pain. *Pain,* Vol. 151, No. 2, pp. (337-344)

Zajicek, J, Fox, P, Sanders, H, Wright, D, Vickery, J, Nunn, A, Thompson, A. (2003). Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet,* Vol. 362, No. 9395, pp. (1517-1526)

Zajicek, JP, Sanders, HP, Wright, DE, Vickery, PJ, Ingram, WM, Reilly, SM, Nunn, AJ, Teare, LJ, Fox, PJ, Thompson, AJ. (2005). Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry,* Vol. 76, No. 12, pp. (1664-1669)



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Neuropathic pain is known to be pain with nerve involvement. The intensity of which depends on the severity, pain threshold and the ability of suffers to cope. Neuropathic pain may need mono-therapy or combination of therapies to be resolved. Neuropathic pain may not resolve completely, therefore patient's compliance and understanding is essential in its management. Awareness and patient's education on targets may be of help during therapies for neuropathic pain. All chapters treated introduction, characteristics, diagnosis and randomized interventions to certain management of neuropathic pain. We acknowledge all those involve in the making of this book.

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