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Therapeutic potential of cannabinoid medicines

P. J. Robson*

Cannabis was extensively used as a medicine throughout the developed world in the nineteenth century but went into decline early in the twentieth century ahead of its emergence as the most widely used illicit recreational drug later that century. Recent advances in cannabinoid pharmacology alongside the discovery of the endocannabinoid system (ECS) have re-ignited interest in cannabis-based medicines. The ECS has emerged as an important physiological system and plausible target for new medicines. Its receptors and endogenous ligands play a vital modulatory role in diverse functions including immune response, food intake, cognition, emotion, perception, behavioural reinforcement, motor co-ordination, body temperature, wake/sleep cycle, bone formation and resorption, and various aspects of hormonal control. In disease it may act as part of the physiological response or as a component of the underlying pathology. In the forefront of clinical research are the cannabinoids delta-9-tetrahydrocannabinol and cannabidiol, and their contrasting pharmacology will be briefly outlined. The therapeutic potential and possible risks of drugs that inhibit the ECS will also be considered. This paper will then go on to review clinical research exploring the potential of cannabinoid medicines in the following indications: symptomatic relief in multiple sclerosis, chronic neuropathic pain, intractable nausea and vomiting, loss of appetite and weight in the context of cancer or AIDS, psychosis, epilepsy, addiction, and metabolic disorders.

Keywords: cannabinoids; endocannabinoid system; medicinal cannabis; tetrahydrocannabinol; cannabidiol

Introduction

Cannabis in the twenty-first century is perceived primarily as the most widely used illegal recreational drug, but this relatively recent notoriety obscures its extensive utilization as a medicine throughout the world for several thousand years. Evidence of its use in treating malaria, constipation, pain, and dysmenorrhoea appear from oral tradition as early as 2600 B.C.E. in China and in following centuries it crops up in pharmacopoeias from Asia, the Middle East, Southern Africa and South America.[1,2] First named *Cannabis sativa* by Leonhardt Fuchs in 1542, it was introduced to British medical practice in the nineteenth century by W.B. O'Shaughnessy as an analgesic, anti-spasmodic, anti-emetic and hypnotic.[3] It entered the United States (US) Dispensatory in 1854 and reached its zenith in Western medicine late in the nineteenth century. The decline of medicinal cannabis began early in the twentieth century as a result of the growing availability of potent synthetic medicines alongside variable potency of these herbal preparations and unreliable sources of supply.

This decline was hastened by increasing concerns about recreational use in some countries, particularly Egypt, South Africa, and the USA. These found political expression at the 1923 League of Nations meeting, and an international convention held in Geneva in 1925 required signatory nations to limit the use of cannabis strictly for medical purposes. Fuelled by lurid propaganda emanating from the newly formed US Bureau of Narcotics (which evolved into the present day Drug Enforcement Administration), cannabis entered the pariah status that remains its lot today. Despite this, the medicinal potential of the plant still induces millions of otherwise law-abiding citizens to use it to relieve their symptoms. This has given rise to many legal anomalies: at the time of writing, 18 US states have decriminalized 'medical marijuana' even though it remains illegal under federal law.

Although there is increasing evidence of the efficacy of smoked or vaporized marijuana in the treatment of a variety of intractable conditions,[4] it is unlikely that any such material will ever obtain regulatory approval for use as a conventional medicine. This paper will therefore focus on pharmaceutical preparations derived from components of cannabis, whether synthetic or plant-derived. Preclinical research has indicated a wide range of potential therapeutic applications for cannabinoid medicines, but only those with at least preliminary evidence of utility in humans will be described in this paper.

The endocannabinoid system (ECS)

The principal psychoactive ingredient of cannabis, delta-9-tetrahydrocannabinol (THC – also known as dronabinol), was identified in 1964.[5] Early attempts to understand its mechanism of action centred largely on electrophysiological data which suggested that euphoria might be due to a depression of inhibitory activity in the septum, cerebellum, and thalamus.[6] Enlightenment came with the discovery in 1988 and subsequent cloning of a specific protein receptor (cannabinoid receptor-1; CB_1R) for THC and its analogues located on nerve cells. The presence of a receptor implies the existence of endogenous ligands and the first of these 'endocannabinoids', N-arachidonoylethanolamine (anandamide), was identified (again by Raphael Mechoulam *et al.*) in 1992.[7] A second ligand, 2-arachidonoylglycerol (2-AG), came to light soon

* *Correspondence to: P. J. Robson, Medical Director, Cannabinoid Research Institute, GW Research Ltd, Porton Down Science Park, Salisbury SP4 0JQ, UK. E-mail: pjr@gwpharm.com*

Cannabinoid Research Institute, GW Research Ltd, Porton Down Science Park, Salisbury SP4 0JQ, UK

after. At about the same time a second cannabinoid receptor (cannabinoid receptor-2; CB_2R), this time on blood cells and immune tissue, was discovered and cloned.[8] The development of specific antagonists for these two receptors permitted detailed evaluation of their physiological roles, and in time the mechanisms for the synthesis, transport, and catabolism of these ligands were ascertained. For a more detailed review of the endocannabinoid system see Di Marzo *et al.*[9]

The CB_1R is the most abundant G protein coupled receptor in the central nervous system (CNS), and is particularly highly expressed in the neocortex, hippocampus, basal ganglia, and cerebellum.[10] Significant densities are also found in certain areas of the brainstem (but not the medullary respiratory centres), spinal cord, and peripheral nerves. This distribution matches quite closely the known pharmacology of THC, which acts as a partial agonist at CB_1Rs. Neurotransmitter release and postsynaptic depolarisation triggers on-demand synthesis of endocannabinoids from arachidonic acid. These travel in a retrograde direction across the synapse to activate presynaptic CB_1Rs which then inhibit further neurotransmitter release through inhibition of adenylate cyclase, mitogen-activated protein kinases, and voltage-activated Ca^{2+} channels, and stimulation of inwardly rectifying K^+ channels. By modulating both excitatory and inhibitory neurotransmitters, this negative feedback system permits fine control of a wide range of physiological functions. Taking into account the additional influence of CB_2Rs, these include immune response, learning, food intake, pain transduction, emotion, perception, behavioural reinforcement, motor co-ordination, body temperature, wake/sleep cycle, hormonal function, bone formation and destruction, and apoptosis.

There is growing evidence that the ECS is deranged in a wide range of medical and psychiatric conditions, either as part of the physiological response or as a component of the underlying pathology.[9] The ECS is thus a plausible target for a novel pharmacological approach to many currently intractable disorders, either by targeting the receptors directly with agonists or antagonists, or by augmenting the endocannabinoids themselves.[9,11]

Pharmacoactive components of cannabis

Over 100 aromatic hydrocarbon compounds unique to the plant have been identified in cannabis resin, and the pharmacology of these 'phytocannabinoids' has recently been reviewed by Russo,[12] and previously by Pertwee.[13] The psychoactivity of cannabis is due to the partial agonist effect of the cannabinoid THC at CB_1Rs in the brain, albeit modulated in various ways by other cannabinoids and plant components. The pharmacology of THC has been extensively studied,[14] and apart from the euphoric effects sought by the recreational user, it has also been shown to act as an analgesic, anti-inflammatory, muscle relaxant, anti-emetic, appetite stimulant, bronchodilator, and to reduce intra-ocular pressure. In laboratory models of neurodegenerative diseases it is neuroprotective. On the negative side, it may produce cognitive impairment, dizziness and tachycardia, alterations in blood pressure, and a range of transient but potentially severe psychiatric effects such as mood change and panic attacks, hallucinations, and delusional beliefs. Depending on the dose and the setting in which it is taken, it can be either anxiolytic or anxiogenic. THC may be teratogenic although the objective evidence for this in humans is not compelling. In cannabis smokers the risk of psychological dependence is roughly equivalent to that of alcohol, but that of physical dependence is much less.[15] In clinical practice to date, the risk of abuse or dependence upon THC-containing medicines appears to be extremely low.[16] Amongst recreational users it has been incriminated as a risk factor for schizophrenia[17] but the level of risk remains controversial. There has been no evidence of an increase in the prevalence of schizophrenia in populations which have experienced very large increases in cannabis consumption.[18]

The principal non-psychoactive cannabinoid in cannabis, cannabidiol (CBD), is currently attracting considerable interest as a potential medicine as a result of its anti-inflammatory, neuroprotective, anti-psychotic, anxiolytic, anti-epileptic, and anti-cancer effects in various *in vitro* and *in vivo* laboratory models. The molecular mechanisms by which it produces these effects remain speculative, but do not seem primarily achieved via cannabinoid receptors. When administered alongside THC it appears to modulate some of its undesirable effects in a medicinal context such as euphoria, tachycardia and cognitive deficits,[19] memory impairment,[20] and psychotic symptoms.[21,22] Functional magnetic resonance imaging in healthy subjects has demonstrated that CBD and THC have oppositional effects in various brain structures implicated in psychiatric disorders, notably the striatum, cingulate and prefrontal cortex, hippocampus and amygdala.[22]

Over-activity of the ECS may be associated with the development of obesity, metabolic problems including Type 2 diabetes mellitus, cardiovascular diseases, and some forms of liver disease. The ECS is also an important modulator of reward processing in the CNS and so has been implicated in addictive behaviour. Rimonabant (also known as SR141716 or Acomplia) is a synthetic drug that acts as an antagonist/inverse agonist at the CB_1R (i.e. it not only blocks the ligand but also reverses the intrinsic, basal or constitutive activity of the receptor producing an opposite pharmacological effect to the agonist), and was introduced as a treatment for the conditions listed above.[23] However, an intact ECS is essential for normal mental health and rimonabant was associated with an increased risk of depression and suicidal ideation. As a result, it was denied regulatory approval in the US and its licence was withdrawn by the European Medicines Agency in 2008. One possible way round this difficulty is the use of a neutral CB_1R antagonist rather than an inverse agonist, since there is evidence that, unlike rimonabant, such agents do not suppress constitutive CB_1R signalling in brain areas controlling emotion and motivation.[24] Tetrahydrocannabivarin (THCV) is a naturally occurring phytocannabinoid which has recently entered early stage clinical trials to investigate its potential in the treatment Type 2 diabetes mellitus.

Various other phytocannabinoids show preliminary evidence of therapeutic potential but are at an early stage of preclinical development. Several of the terpenoids that occur naturally in cannabis are pharmacologically active and appear to synergise with phytocannabinoids in certain therapeutic applications.[12] This 'entourage' effect is an important potential advantage of medicines based on medicinal plant extracts rather than synthetic single chemical entities.

Clinical targets for cannabinoid medicines:

THC-containing medicines

Symptomatic relief in multiple sclerosis (MS) and other neurological effects. Current treatments for MS-related symptoms such as muscle spasticity and spasms, neuropathic pain, tremor, ataxia,

and neurogenic bladder problems are often unsatisfactory in terms of efficacy and tolerability.[25] Anecdotal reports[2] and findings in laboratory models of MS[26,27] suggested that cannabis or cannabinoids showed promise in a range of these symptoms, and some small-scale pioneering clinical studies were also encouraging,[28–32] whilst others failed to show a benefit.[33,34] The findings encouraged the United Kingdom (UK) Medical Research Council to fund a large (n = 630) placebo-controlled trial exploring the effect of THC and a cannabis extract (Cannador) on various MS symptoms following 15 weeks of treatment, and the results were rather mixed.[35] There was no significant benefit on the primary outcome variable, the Ashworth scale for spasticity, although this measure has in recent years been largely discredited.[36] On the other hand, numerical rating scale (NRS) measures of spasticity, muscle spasms, pain and sleep, and an objective measure of mobility all showed a significant benefit of both active treatments compared with placebo. No benefit was recorded for irritability, depression, tiredness, tremor or loss of energy. The active treatments were well tolerated. Zajicek *et al.* recruited 80% of the patients from this trial into a 12-month maintenance study which suggested that cannabinoids may offer longer term benefits with no safety concerns.[37] Subsequently, the same investigators carried out a further 12-week treatment trial comparing Cannador with placebo in 277 MS patients. Significant improvements in muscle stiffness, body pain, muscle spasms and sleep quality were reported for the active treatment group in comparison with placebo with no new safety concerns.[38]

Sativex® is a novel, plant-derived standardized cannabinoid medicine administered as an oromucosal spray delivering 2.7 mg THC and 2.5 mg CBD per activation that has been extensively investigated in the treatment of MS patients. Only patients who had failed to respond to standard treatments were eligible for the Sativex® clinical trial programme, and Sativex® or placebo was in all cases added to the existing medication. Exploratory trials in several hundred patients consistently showed significant advantages for Sativex® over placebo in the relief of spasticity, chronic pain, muscle spasms, bladder-related problems and sleep quality which appeared to be maintained over long-term treatment, and the medicine was generally well tolerated.[39–48] The focus on refractory patients inevitably recruited a proportion of subjects who would be non-responders to any intervention, so that the degree of improvement in those able to benefit from the drug is obscured. The largest study of Sativex® published to date addressed this problem by adopting an 'enriched' design. Novotna *et al.*[49] recruited 572 refractory MS patients into a 4-week, single-blind period of treatment with Sativex® in addition to their existing medicine. Only those subjects who demonstrated at least a 20% improvement from baseline in spasticity over this period progressed into the second phase of the study. These subjects (n = 272) entered a 12-week, randomized, parallel group double-blind comparison of Sativex® and placebo. A highly significant (p = 0.0002) benefit in spasticity score (NRS) was reported for Sativex® in comparison with placebo, along with significant improvements in spasm frequency, sleep disturbance and global impression of change. Overall, the adverse event rate was similar between Sativex® and placebo, the most common events on the active drug being vertigo, fatigue, muscle spasms and urinary tract infection. On the basis of the collective results, Sativex® was granted regulatory approval in the UK and Spain for the treatment of MS spasticity in 2010 and subsequently in a further 19 countries.

It is plausible that cannabinoids may be useful for symptomatic relief in other neurological disorders but convincing clinical evidence is not yet available. The situation for Tourette's syndrome is typical: although there are numerous anecdotal reports and two small clinical trials indicating a beneficial effect of THC, a Cochrane review indicated that there was currently insufficient evidence to support its use.[50] Disturbed sleep is a cause of much distress and additional morbidity in many chronic diseases, and there is evidence that Sativex® consistently ameliorates this.[51] The authors of this review speculate that this is probably due to nocturnal symptomatic relief rather than a direct hypnotic effect.

Although there are as yet no clinical data, there is growing evidence from laboratory studies that THC and other cannabinoids, notably CBD, have neuroprotective properties as a result of their anti-oxidant, anti-inflammatory and anti-excitotoxic properties which may prove disease modifying in MS and other neurodegenerative conditions.[52]

Chronic pain. Anecdotal reports notwithstanding,[2] the clinical research addressing the use of cannabinoids in nociceptive pain is not particularly compelling, but for neuropathic pain the picture is more encouraging. This type of pain is generally recognised as difficult to treat[53] but there is good laboratory evidence in support of a cannabinoid approach.[54] Pioneering clinical studies have shown efficacy of THC, nabilone (a THC analogue) and Sativex® in comparison with placebo in human neuropathic pain of various aetiologies. [40,43,48,55–58] Sativex® proved significantly superior to placebo on pain scores (p = 0.005) and improvement in sleep (p = 0.003) in a double-blind trial in MS patients with intractable central neuropathic pain over 4 weeks of treatment.[43] Regulatory approval for this indication was granted in Canada in 2005 mainly on the basis of these results. Rog *et al.* recruited 95% of the acute sample into a long-term, open-label follow up study.[48] Mean duration of treatment was 463 days (range 3–917), during which Sativex® efficacy was retained with no tolerance in those maintained on the drug for at least two years, with the most common adverse effects being dizziness and nausea. A later study in MS-related central neuropathic pain gave equivocal results: an initial placebo-controlled trial over 14 weeks of treatment showed no advantage for Sativex® over placebo, but a subsequent randomized withdrawal trial showed significant advantages for the active drug in terms of time to treatment failure, pain, and sleep scores.[47] Sativex® has also been evaluated in a double-blind, randomised, placebo-controlled trial over five weeks of treatment in 125 patients with peripheral neuropathic pain of mixed aetiology.[59] Significant improvements following Sativex® compared with placebo were reported in pain intensity NRS scores (p = 0.004), Neuropathic Pain Scale composite score (p = 0.007), sleep NRS scores (p = 0.001), dynamic (p = 0.042) and punctate (p = 0.021) allodynia test scores, Pain Disability Index scores (p = 0.003) and patient's global impression of change (p = 0.001). An open-label extension study indicated that benefits were maintained without any evidence of tolerance. The commonest unwanted effects on Sativex® were dizziness, nausea, and fatigue.

Pioneering exploratory trials indicated that THC produced dose-related relief of cancer pain superior to placebo and equivalent to codeine, albeit at the expense of sedation and 'mental clouding' in most patients.[60,61] More recently, Sativex® has been evaluated in two larger clinical trials.[62,63] Johnson *et al.* compared the drug with THC whole-plant extract and placebo as an add-on treatment in a two-week parallel group, randomized double-blind trial in 177 patients with opioid-resistant pain resulting

from advanced cancer.[62] Both THC extract and Sativex® were superior to placebo in the primary outcome measure of NRS pain score, but only the Sativex® group was statistically significantly better than placebo. Sativex® produced twice as many 'responders' as THC extract (defined as a reduction of pain score > 30% from baseline). However, it produced a significant worsening in nausea and vomiting whilst THC extract did not differ in this regard from placebo. A longer-term, open-label follow up trial was conducted in 43 of these patients.[63] Pain scores, insomnia, and fatigue continued to improve over the median 25 days of treatment (range 2–579 days) with no evidence of tolerance developing. Portenoy *et al.* assessed the effect of different doses of Sativex® in refractory cancer pain.[64] A total of 360 patients were randomized in a double-blind manner to receive low (1–4 sprays/day), medium (6–10 sprays/day) or high (11–16 sprays/day) doses of Sativex® or placebo as an add-on treatment over five weeks of treatment. Overall, the 30% responder rate (in NRS average pain scores) was similar for Sativex® and placebo, but continuous responder analysis suggested that the low and middle doses were superior ($p = 0.008$ and 0.039, respectively). Adverse events were dose-related and the high-dose group compared unfavourably with placebo.

Inflammatory pain is a logical target for cannabinoid medicines since, alongside analgesic properties, the anti-inflammatory effects of both THC and CBD are well established in the laboratory.[65] This was an important historical target for cannabis as a medicine, and modern surveys amongst medicinal cannabis users indicate a sizeable proportion targeting arthritis.[66] CBD not only produced functional improvement and joint protection in a murine model of arthritis but also inhibited disease progression.[67] Only a single controlled trial has so far been completed. Sativex® was compared with placebo in a randomized, double-blind parallel group trial in 58 patients with rheumatoid arthritis (RA) over 5 weeks of treatment.[68] In comparison with placebo, Sativex® produced significant improvements in pain on movement and at rest, and in quality of sleep. Unwanted effects were well tolerated and did not result in any withdrawals from the trial. Of particular note over such a short period of treatment, Sativex® significantly improved the standard measure of RA disease activity (DAS28), raising the possibility of disease modification.

Nausea and vomiting. There is abundant laboratory evidence that CB_1R agonism suppresses vomiting, and that THC and CBD alleviate both nausea and vomiting albeit via different pharmacological mechanisms.[69] A large number of clinical studies in the 1970s and 1980s confirmed this attribute, notably in the relief of cytotoxic chemotherapy-induced vomiting. Reviews have confirmed consistent statistically significant benefits of THC or nabilone in comparison with placebo, with mild to moderate sedation or psychoactivity being the most common unwanted effects.[70–72] Regulatory approval for one or both of these cannabinoids in this indication was granted in many countries including the USA and the UK. However, the introduction of the serotonin 5-HT3 receptor antagonists in the 1990s completely transformed the treatment of severe nausea and vomiting. Cannabinoids are therefore no longer indicated for first-line treatment, and are now generally reserved for patients with non-responsive or breakthrough nausea and vomiting.[73] There is preliminary evidence that in patients experiencing intractable chemotherapy-induced nausea and vomiting the addition of Sativex® to the standard anti-emetic regime may improve outcome.[74]

Appetite stimulation. Often observed by recreational users ('the munchies'), cannabis stimulates appetite and the same is well established to be the case with THC and other CB_1R agonists.[75] Loss of appetite and progressive weight loss is a common feature of cancer and acquired immune deficiency syndrome (AIDS). A randomised, double-blind placebo-controlled clinical trial in 139 AIDS patients showed that a small oral dose of THC (5 mg) significantly improved appetite ($p < 0.015$) and nausea ($p = 0.05$) in comparison with placebo, and also showed signs of lifting mood and increasing weight.[76] Euphoria, dizziness, 'thinking abnormalities', and sedation were common unwanted effects, usually of only mild to moderate severity. A one-year follow-up trial showed that appetite improvements were well maintained with no increase in dose, and unwanted effects were well tolerated.[77] THC-containing medicines are also likely to prove helpful for other symptoms commonly experienced by AIDS patients including nausea, pain and insomnia. Concern has been expressed that the immunosuppressive effects of THC might prove deleterious in AIDS, but investigation has revealed no impairment of the drug on T cell levels or activation or any other aspect of immune function, nor any evidence of increased viral load.[78–80]

The evidence supporting THC use in cancer-related weight loss is less clear cut. Exploratory trials suggested a positive effect on appetite and weight,[72,81,82] but a larger trial indicated that THC (2.5 mg twice daily) was significantly inferior to megestrol for improving appetite and weight, and did not improve the outcome if added to megestrol.[83] However, impotence was a significant problem for megestrol-treated men, and the very low levels of unwanted effects with THC suggest a sub-optimal dose was used in this trial. Finally, a randomized double-blind trial in 243 cancer patients demonstrated no difference between THC 2.5 mg or a cannabis extract standardised to THC content 2.5 mg and placebo in terms of appetite or quality of life.[84] However, as in the previous study, the incidence of adverse events was similar for the active groups and placebo, suggesting that the chosen dose of THC was far too low.

It is plausible that THC may improve appetite in other chronic, wasting conditions and some evidence exists that this is the case in Alzheimer's disease.[85,86]

CBD medicines

Psychosis. Pioneering early studies in healthy humans demonstrated that CBD could inhibit the cognitive and psychotomimetic effects of THC.[19,87] Its anti-psychotic potential has subsequently been repeatedly demonstrated in dopamine and glutamate models of psychosis in both animals and humans.[88–90] The presence of significant amounts of CBD in street cannabis (an increasingly uncommon phenomenon) has been shown to protect users against both psychotic symptoms [21] and memory impairment.[20] Studies in humans using functional magnetic resonance imaging of the brain have demonstrated that these effects are related to the oppositional effects of THC and CBD in key areas of interest for schizophrenia including the striatum, prefrontal cortex and hippocampus.[91]

Single case reports of the use of CBD in schizophrenia patients have given mixed results, but the only clinical trial conducted to date has been encouraging. Leweke *et al.* compared the effects of CBD and a standard anti-psychotic (amisulpride) in a double-blind, randomized, parallel-group study in 42 schizophrenia patients over a treatment period of 4 weeks.[92] Both treatments produced a marked and equivalent improvement in psychotic symptoms from baseline, and there were significant advantages for CBD in terms of adverse event profile. The mechanism of this anti-psychotic action of CBD is currently unknown, although there are several theories

(recently reviewed by Robson *et al.* [93]). However, it is clear that it differs from all existing anti-psychotics in not primarily targeting the dopamine D2 receptor in the striatum. A synergistic effect with standard drugs is therefore plausible.

Schizophrenia is not merely a disorder of the brain but is also associated with natural and iatrogenic metabolic abnormalities, and evidence of chronic systemic inflammation.[93] Since laboratory evidence suggests that CBD may have a significant impact on both of these areas, it appears to have the potential to prove a useful medicine for both the psychological and physical manifestations of the disease.

Epilepsy. This was an important historical target for medicinal cannabis.[3] Modern research has shown that the ECS in the CNS plays an important role in modulating seizure activity and regulating neuroexcitation.[94] Several cannabinoids have been shown in laboratory studies to have significant anti-convulsive properties, most notably CBD [95] and more recently its naturally occuring propyl analogue cannabidivarin (CBDV).[96] CBDs mechanism of action as an anti-convulsant is unknown; however, it appears to act independently of the ECS.[95]

Human research is still in its infancy. Apart from a small number of case reports which give conflicting results, there have been four placebo-controlled clinical trials involving only 48 refractory patients in total. All have focused on CBD as add-on medication at doses of 200–300 mg/day over treatment periods ranging from four weeks to twelve months.[97–100] Three out of these four trials reported some reduction in seizures in the CBD group but of course no statistical comparison with placebo was possible with such small numbers. CBD was very well tolerated: in three of the trials no unwanted effects were reported, and in the fourth a few patients experienced 'mild drowsiness'.

Based on the encouraging preclinical literature and human safety profile, there is a strong case for exploring the potential of both CBD and CBDV in properly controlled randomized clinical trials.

CB_1R antagonists

Large-scale clinical trials demonstrated that in comparison with placebo, the CB_1R antagonist/inverse agonist rimonabant consistently induced weight loss in obese subjects along with improvements in metabolic parameters such as reduction in glycosylated haemoglobin levels, improved lipidaemic profile, and increases in serum adiponectin.[101] Other large trials also demonstrated that it significantly improved the success of achieving and maintaining abstinence in tobacco smokers, and it was also noted that associated weight gain was significantly lower in the rimonabant group in comparison with placebo.[102] Unfortunately, these beneficial effects were accompanied by a significantly increased incidence of depression, anxiety, nausea, and dizziness. The psychiatric effects prevented rimonabant ever receiving regulatory approval in the USA, and led to the withdrawal of approval by the European Medicines Agency in 2008. Although this body blow ended all research focused on rimonabant (and tarabant, a similar compound), more recently it has become evident that neutral CB_1R antagonists retain the positive attributes of rimonabant[103] but do not suppress the constitutive CB_1R activity which modulates excitatory and inhibitory transmission in the ventral tegmental area and basolateral amygdala, brain regions which regulate motivation and emotional response.[24] Thus it seems likely that synthetic (e.g. AM4113[103]) or plant derived (e.g. THCV[104]) CB_1R neutral antagonists will soon emerge into clinical trials in the context of addiction and metabolic disorders.

Conflicts of interest

The author is affiliated to GW Pharmaceuticals, a public company that is researching and developing a portfolio of cannabinoid medicines.

References

[1] R. Mechoulam. The pharmacohistory of cannabis sativa, in *Cannabinoids as Therapeutic Agents*, (Ed: R. Mechoulam). CRC Press, Roca Raton, **1986**, pp. 1–19.
[2] L. Grinspoon, J.B. Bakalar, Cannabis as a medicine, in *Marijuana: The Forbidden Medicine*. Yale University Press: New Haven, **1993**, pp. 67–81.
[3] W.B. O'Shaughnessy. On the cannabis indica or Indian hemp. *Pharmacol. J.* **1843**, *2*, 594.
[4] I. Grant, J. H. Atkinson, B. Gouaux, B. Wilsey. Medical marijuana: Clearing away the smoke. *Open Neuro. J.* **2012**, *6*, 18.
[5] Y. Gaoni, R. Mechoulam. Isolation, structure, and partial synthesis of an active constituent of hashish. *J. Am. Chem. Soc.* **1964**, *86*, 1646.
[6] W.D.M. Paton. The pharmacology of marijuana. *Annu. Rev. Pharmacol.* **1975**, *15*, 191.
[7] W. A. Devane, L. Hanus, A. Breuer, R. G. Pertwee, L. A. Stevenson, G. Griffin, *et al.* Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* **1992**, *258*(5090), 1946.
[8] S. Munro, K. L. Thomas, M. Abu-Shaar. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*(6441), 61.
[9] V. Di Marzo, M. Bifulco, L. De Petrocellis. The endocannabinoid system and its therapeutic exploitation. *Nat. Rev.* **2004**, *3*, 771.
[10] K. Mackie, Distribution of cannabinoid receptors in the central and peripheral nervous system, in *Cannabinoids*, (Ed. R. Pertwee). Springer-Verlag, Berlin Heidelberg, **2005**, pp. 299–325.
[11] P. Pacher, S. Batkai, G. Kunos. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol. Rev.* **2006**, *58*, 389.
[12] E. B. Russo. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Brit. J. Pharmacol.* **2011**, *163*, 1344.
[13] R. G. Pertwee. Cannabinoid pharmacology: The first 66 years. *Brit. J. Pharmaocol.* **2006**, *147*, S163.
[14] B. Costa. On the pharmacological properties of delta-9-tetrahydrocannabinol (THC). *Chem. Biodivers.* **2007**, *4*, 1664.
[15] D. Nutt, L. A. King, W. Saulsbury, C. Blakemore. Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* **2007**, *369*, 1047.
[16] P. Robson. Abuse potential and psychoactive effects of Δ-9-tetrahydrocannabinol and cannabinoid oromucosal spray (Sativex), a new cannabinoid medicine. *Exp. Opin. Drug Saf.* **2011**, *10*, 1.
[17] D. C. D'Souza, R. A. Sewell, M. Ranganathan. Cannabis and psychosis/schizophrenia: Human studies. *Eur. Arch. Psy. Clin. N.* **2009**, *259*, 413.
[18] M. Frisher, I. Crome, O. Martino, P. Croft. Assessing the impact of cannabis use on trends in diagnosed schizphrenia in the United Kingdom from 1996 to 2005. *Schizophr. Res.* **2009**, *113*, 123.
[19] I. G. Karniol, I. Shirakawa, N. Kasinski, A. Pfeferman, E. A. Carlini. Cannabidiol interferes with the effect of Δ^9-tetrahydrocannabinol in man. *Eur. J. Pharmacol.* **1974**, *28*(1), 172.
[20] C. J. A. Morgan, G. Schafer, T. P. Freeman, H. V. Curran. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: Naturalistic study. *Brit. J. Psych.* **2010**, *197*, 285.
[21] C. J. A. Morgan, H. V. Curran. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Brit. J. Psychol.* **2008**, *192*, 306.
[22] S. Bhattacharyya, P. D. Morrison, P. Fusar-Poli, R. Martin-Santos, S. Borgwardt, T. Winton-Brown, *et al.* Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* **2010**, *35*, 764.
[23] M. Bifulco, C. Grimaldi, P. Gazzero, S. Pisanti, A. Santoro. Rimonabant: Just an anti-obesity drug? Current evidence on its pleiotropic effects. *Mol. Pharmacol.* **2007**, *71*, 1445.
[24] F. J. Meye, V. Trezza, L. J. Vanderschuren, G. M. Ramakers, R. A. Adan. Neutral antagonism at the cannabinoid 1 receptor: A safer treatment for obesity. *Mol. Psychiatr.* **2012**, DOI: 10.1038/mp.2012.145
[25] A. J. Thompson. Symptomatic management and rehabilitation in multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* **2001**, *71, S2:ii*, 22.

[26] D. Baker, G. Pryce, J. L. Croxford, P. Brown, R.G. Pertwee, J.W. Huffman, *et al.* Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* **2000**, *404*, 84.

[27] A. Hilliard, C. Stott, S. Wright, G. Guy, G. Pryce, S. Al-Izki, *et al.* Evaluation of the effects of Sativex (THC BDS: CBD BDS) on inhibition of spasticity in a chronic relapsing experimental allergic autoimmune encephalomyelitis: A model of multiple sclerosis. *ISRN Neurol.* **2012**, DOI: 10.5402/2012/802649

[28] D. J. Petro, C. Ellenberger. The treatment of human spasticity with delta-9-THC. *J. Clin. Pharmacol.* **1981**, *21*, 413.

[29] D. B. Clifford. THC for tremor in multiple sclerosis. *Ann. Neurol.* **1983**, *13*, 669.

[30] H. M. Meinck, P. W. Schonle, B. Conrad. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *J. Neurol.* **1989**, *236*, 120.

[31] R. Brenneissen, A. Egli, M. A. Elsohly, V. Henn, Y. Spiess. The effect of orally and rectally administered delta-9-THC on spasticity: A pilot study with two patients. *Int. J. Clin. Pharm. Th.* **1996**, *34*, 446.

[32] P. Consroe, R. Musty, J. Rein, W. Tillery, R. Pertwee. The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur. Neurol.* **1997**, *38*, 44.

[33] C. Vaney, P. Jobin, F. Tschopp, M. Heinzel, M. Schnelle. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis, in *Symposium of the Cannabinoids, International Cannabinoid Research Society*. **2002**, pp. 57.

[34] J. Killestein, E. L. Hoogervorst, M. Reif, N. F. Kalkers, A. C. Van Loenen, P. G. Staats, *et al.* Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* **2002**, *58*, 1404.

[35] J. Zajicek, P. Fox, H. Sanders, D. Wright, J. Vickery, A. Nunn, *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): Multicentre randomised placebo-controlled trial. *Lancet* **2003**, *362*, 1517.

[36] J. F. Fleuren, G. E. Voerman, C. V. Erren-Wolters, G. J. Snoek, J. S. Rietman, H. J. Hermens, *et al.* Stop using the Ashworth scale for the assessment of spasticity. *J. Neurol. Neurosurg. Psychiat.* **2010**, *81*, 46.

[37] J. P. Zajicek, H. P. Sanders, D. E. Wright, P. J. Vickery, W. M. Ingram, S. M. Reilly, *et al.* Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J. Neurol. Neurosurg. Psychiat.* **2005**, *76*, 164.

[38] J. P. Zajicek, J. C. Hobart, A. Slade, D. Barnes, P. G. Mattison. Multiple sclerosis and extract of cannabis: Results of the MUSEC trial. *J. Neurol. Neurosurg. Psychiat.* **2012**, *83*, 1125.

[39] D. T. Wade, P. Robson, H. House, P. Makela, J. Aram. A preliminary controlled study to determine whether whole plant cannabis extracts can improve intractable neurogenic symptoms. *Clin. Rehab.* **2003**, *17*, 18.

[40] D. T. Wade, P. Makela, H. House, C. Bateman, P. Robson. 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. J.* **2004**, *10*, 434.

[41] D. T. Wade, P. M. Makela, H. House, C. Bateman, P. Robson. Long-term use of a cannabinoid-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult. Scler. J.* **2006**, *12*, 639.

[42] C. M. Brady, R. DasGupta, C. Dalton, O. J. Wiseman, K. J. Berkley, C. J. Fowler. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult. Scler. J.* **2004**, *10*, 425.

[43] D. J. Rog, T. J. Nurmikko, T. Friede, C. A. Young. Randomised, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* **2005**, *65*, 812.

[44] C. Collin, P. Davies, I. K. Mutiboko, S. Ratcliffe, Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur. J. Neurol.* **2007**, *14*, 290.

[45] R. B. C. Kavia, C. De Ridder, C. S. Constantinescu, *et al.* Randomised controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. *Mult. Scler. J.* **2010**, *16*, 1349.

[46] M. G. Serpell, W. Notcutt, C. Collin. Sativex long-term use: An open-label trial in patients with spasticity due to multiple sclerosis. *J. Neurol.* **2013**, *260*(1), 285.

[47] R. M. Langford, J. Mares, A. Novotna, M. Vachova, I. Novakova, W. Notcutt, *et al.* Ratcliffe. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J. Neurol.* **2013**, *260*(4), 984.

[48] D. J. Rog, T. J. Nurmikko, C. A. Young. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: An uncontrolled, open-label, 2-year extension trial. *Clin. Ther.* **2007**, *29*(9), 2068.

[49] A. Novotna, J. Mares, S. Ratcliffe, I. Novakova, M. Vachova, O. Zapletalova, *et al.* A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur. J. Neurol.* **2011**, *18*, 1122.

[50] A. Curtis, C. E. Clarke, H. E. Rickards. Cannabinoids for Tourette's syndrome. *Cochrane Database Syst. Rev.* **2009**, DOI: 10.1002/14651858.CD006565.pub2

[51] E. B. Russo, G. W. Guy, P. J. Robson. Cannabis, pain and sleep: Lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem. Biodivers.* **2007**, *4*, 1729.

[52] E. de Lago, J. Fernandez-Ruiz. Cannabinoids and neuroprotection in motor-related disorders. *CNS Neurol. Disord. Drug Targets* **2007**, *6*, 377.

[53] R. Freynhagen, M. I. Bennett. Diagnosis and management of neuropathic pain. *Brit. Med. J.* **2009**, *339*, b3002.

[54] J. M. Walker, A. G. Hohmann, Cannabinoid mechanisms of pain suppression, in *Cannabinoids*, (Ed: R. Pertwee). Springer-Verlag, Berlin, Heidelberg, **2005**, pp. 509–554.

[55] W. Notcutt, M. Price, G. Chapman. Clinical experience with nabilone for chronic pain. *Pharm. Sci.* **1997**, *3*, 551.

[56] K. B. Svendsen, T. S. Jensen, F. W. Bach. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *Brit. Med. J.* **2004**, *329*, 253.

[57] W. Notcutt, M. Price, R. Miller, S. Newport, C. Phillips, S. Simmons, *et al.* Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'n of 1' studies. *Anaesthesia* **2004**, *59*, 440.

[58] J. S. Berman, C. Symonds, R. Birch. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: Results of a randomised controlled trial. *Pain* **2004**, *112*, 29.

[59] T. J. Nurmikko, M. G. Serpell, B. Hoggart, P. J. Toomey, B. J. Morlion, D. Haines. Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. *Pain* **2007**, *133*, 210.

[60] R. Noyes, S. F. Brunk, D. A. Baram, A. Canter. Analgesic effects of delta-9-THC. *J. Clin. Pharmacol.* **1975**, *15*, 139.

[61] R. Noyes, S. F. Brunk, D. H. Avery, A. Canter. The analgesic properties of delta-9-THC and codeine. *Clin. Pharmacol. Ther.* **1975**, *18*, 84.

[62] J. R. Johnson, M. Burnell-Nugent, D. Lossignol, E. D. Ganae-Motan, R. Potts, M. T. Fallon. Multicenter, double-blind, randomised, placebo-controlled, parallel-group study of the efficacy, safety and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J. Pain Symptom Manag.* **2010**, *39*, 167.

[63] J. R. Johnson, D. Lossignol, M. Burnell-Nugent, M. T. Fallon. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. *J. Pain Symptom Manag.* **2012**, DOI: pii: S0885-3924(12)00439-3

[64] R. K. Portenoy, E. D. Ganae-Motan, S. Allende, R. Yanagihara, L. Shaiova, S. Weinstein, *et al.* Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: A randomized, placebo-controlled, graded-dose trial. *Pain* **2012**, *13*, 438.

[65] T. W. Klein. Cannabinoid-based drugs as anti-inflammatory therapeutics. *Nat. Rev. Immunol.* **2005**, *5*, 400.

[66] M. A. Ware, H. Adams, G. W. Guy. The medicinal use of cannabis in the UK: Results of a nationwide survey. *Int. J. Clin. Pract.* **2005**, *59*, 291.

[67] A. M. Malfait, R. Gallily, P. F. Sumariwalla, A. S. Malik, E. Andreakos, R. Mechoulam, *et al.* The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*(17), 9561.

[68] D. R. Blake, P. Robson, M. Ho, R. W. Jubb, C. S. McCabe. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* **2006**, *45*, 50.

[69] L. A. Parker, E. M. Rock, C. L. Limebeer. Regulation of nausea and vomiting by cannabinoids. *Brit. J. Pharmacol.* **2011**, *163*, 141.
[70] J. S. Penta, D. S. Poster, S. Bruno, J. S. Macdonald. Clinical trials with anti-emetic agents in cancer patients receiving chemotherapy. *J. Clin. Pharmacol.* **1981**, *21*, 11.
[71] M. Levitt, Cannabinoids as antiemetics in cancer chemotherapy, in *Cannabinoids as Therapeutic Agents*. (Ed: R. Mechoulam), CRC Press, Boca Raton, **1986**, pp. 71–83.
[72] T. F. Plasse, R. W. Gorter, S. H. Krasnow, M. Lane, K. V. Shepard, R. G. Wadleigh. Recent clinical experience with dronabinol. *Pharmacol. Biochem. Be.* **1991**, *40*, 695.
[73] B. Todaro. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. *J. Natl. Compr. Canc. Netw.* **2012**, *10*, 487.
[74] M. Duran, E. Pérez, S. Abanades, X. Vidal, C. Saura, M. Majem, *et al.* Preliminary efficacy and safety of an oromucosal standardised cannabis extract in chemotherapy-induced nausea and vomiting. *Brit. J. Clin. Pharm.* **2010**, *70*(5), 656.
[75] T. C. Kirkham, C. M. Williams. Endogenous cannabinoids and appetite. *Nutr. Res. Rev.* **2001**, *14*, 65.
[76] J. E. Beal, R. Olson, L. Laubenstein, J. O. Morales, P. Bellman, B. Yangco, *et al.* Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J. Pain Symptom Manag.* **1995**, *10*, 89.
[77] J. E. Beal, R. Olson, L. Lefkowitz, L. Laubenstein, P. Bellman, B. Yangco, *et al.* Long-term efficacy and safety of dronabinol for acquired immuned deficiency syndrome-associated nausea. *J. Pain Symptom Manag.* **1997**, *21*, 214.
[78] R. A. Kaslow, W. C. Blackwelder, D. G. Ostrow, D. Yerg, J. Palenicek, A. H. Coulson, *et al.* No evidence for a role of alcohol or other psychoactive drugs in accelerating immune deficiency in HIV-1 positive individuals. *JAMA* **1989**, *261*, 3424.
[79] B. M. Bredt, D. Higueral-Alhino, S. B. Shade, S. J. Hebert, J. M. McCune, D.I. Abrams. Short term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *J. Clin. Pharmacol.* **2002**, *42*, 82.
[80] D. I. Abrams, J. F. Hilton, R. J. Leiser, S. B. Shade, T. A. Elbeik, F. T. Aweeka, *et al.* Short-term effects of cannabinoids in patients with HIV-1 infection. A randomized, placebo-controlled clinical trial. *Ann. Intern. Med.* **2003**, *139*, 258.
[81] W. Regelson, J. R. Butler, J. Schulz, T. Kirk, L. Peek, M. L. Green, *et al.* Delta-9-THC as an effective antidepressant and appetite-stimulating agent in advanced cancer patients, in *The Pharmacology of Marijuana*. (Eds. M.C. Braude, S. Szara), Raven Press, New York, **1976**, pp. 763–775.
[82] K. Nelson, D. Walsh, P. Deeter, F. Sheehan. A phase-II study of delta-9-THC for appetite-stimulation in cancer-associated anorexia. *J. Palliat. Care* **1994**, *10*, 14–18.
[83] A. Jatoi, H. E. Windschitl, C. L. Loprinzi, J. A. Sloan, S. R. Dakhil, J. A. Mailliard, *et al.* Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia. *J. Clin. Oncol.* **2002**, *29*, 567.
[84] Cannabis-In-Cachexia-Study-Group, F. Strasser, D. Luftner, K. Possinger, G. Ernst, T. Ruhstaller, *et al.* Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: A multcenter, Phase III, randomized, double-blind, placebo-controlled clinical trial from cannabis-in-cachexia-study-group. *J. Clin. Oncol.* **2006**, *24*, 3394.
[85] L. Volicer, M. Stelly, J. Morris, J. McLaughlin, B. J. Volicer. Effects of dronabinol on anorexia and disturbed behaviour in patients with Alzheimer's disease. *Int. J. Geriatr. Psych.* **1997**, *12*, 913.
[86] S. Patel, J. R. Shua-Haim, M. Pass. Safety and efficacy of dronabinol in the treatment of agitation in patients with Alzheimer's disease and anorexia: A retrospective chart review, *Eleventh International Congress of the International Psychogeriatric Association*, Chicago, August 17-22, **2003**.
[87] A. W. Zuardi, I. Shirakawa, E. Finkelfarb, I. G. Karniol. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl)* **1982**, *76*(3), 245.
[88] A. W. Zuardi, J. A. Rogdrigues, J. M. Cunha. Effects of cannabidiol in animal models predictive of antipsychotic activity. *Psychopharmacology (Berl)* **1991**, *104*, 260.
[89] D. C. Bosi, J. E. Hallak, S. M. Dursun, J. F. Deakin, A. W. Zuardi. Effects of cannabidiol on (s)-ketamine-induced psychopathology in healthy volunteers. *J. Psychopharmacol.* **2003**, *17*, A55.
[90] L. E. Long, D. T. Malone, D. A. Taylor. Cannabidiol reverses MK-801-induced disruption of prepulse inhibition in mice. *Neuropsychopharmacology* **2006**, *31*, 795.
[91] S. Bhattacharyya, J. A. Crippa, P. Allen, R. Martin-Santos, S. Borgwardt, P. Fusar-Poli, *et al.* Induction of psychosis by delta-9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. *Arch. Gen. Psychiat.* **2012**, *69*(1), 27.
[92] F. M. Leweke, D. Piomelli, F. Pahlisch, D. Muhl, C. W. Gerth, C. Hoyer, *et al.* Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl. Psychiatry* **2012**, DOI:10.1038/tp.2012.15
[93] P. J. Robson, G. W. Guy, V. Di Marzo. Cannabinoids and schizophrenia: Therapeutic prospects. *Curr. Pharm. Design* **2013**, Jun 14. Epub ahead of print http://www.ncbi.nlm.nih.gov/pubmed/23829368
[94] M. J. Wallace, B. E. Blair, W. Falenski, B. R. Martin, R. J. DeLorenzo. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J. Pharm. Exp. Ther.* **2003**, *307*, 129.
[95] N. A. Jones, A. J. Hill, I. Smith, S. A. Bevan, C.M. Williams, B. J. Whalley, *et al.* Cannabidiol displays antiepileptoform and antiseizure properties in vitro and in vivo. *J. Pharm. Exp. Ther.* **2010**, *332*, 569.
[96] A. J. Hill, M. S. Mercier, T. D. Hill, S. E. Glyn, N. A. Jones, Y. Yamasaki, *et al.* Cannabidivarin is anticonvulsant in mouse and rat. *Brit. J. Pharmacol.* **2012**, *167*, 1629.
[97] J. M. Cunha, E. A. Carlini, A. E. Pereira, O. L. Ramos, C. Pimentel, R. Gagliardi, *et al.* Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* **1980**, *21*, 175.
[98] F. R. Ames, S. Cridland. Anticonvulsant effect of cannabidiol. *S. Afr. Med. J.* **1985**, *69*, 14.
[99] B. Trembly, M. Sherman. Double blind clinical study of cannabidiol as a secondary anticonvulsant. *Marijuana '90 International Conference on Cannabis and Cannabinoids*, 8–11 July, 1990; Kolympari, Crete, International Association for Cannabinoid Medicines, **1990**, pp. 5.
[100] Mechoulam R., Carlini E.A. Toward drugs derived from cannabis. *Naturwissenschaften* **1978**, *65*, 174.
[101] F. D. Christopoulou, D. N. Kiortis. An overview of the metabolic effects of rimonabant in randomized controlled trials: Potential for other cannabinoid 1 receptor blockers in obesity. *J. Clin. Pharm. Ther.* **2011**, *36*, 10.
[102] K. Cahill, M. H. Ussher. Cannabinoid type 1 receptor antagonists for smoking cessation (review). *The Cochrane Library* **2012**. The Cochrane Collaboration, Issue 7. Published by JohnWiley & Sons, Ltd.
[103] B. D. Kangas, M. S. Delatte, V. K. Vemuri, G. A. Thakur, S. P. Nikas, K. V. Subramanian, *et al.* Cannabinoid discrimination and antagonism by CB1 neutral and inverse agonist antagonists. *J. Pharm. Exp. Ther.* **2013**, *344*, 561.
[104] E. T. Wargent, M. S. Zaibi, C. Silvestri, D. C. Hislop, C. J. Stocker, C. G. Stott, *et al.* The cannabinoid D9-tetrahydrocannabivarin (THCV) ameliorates insulin sensitivity in two mouse models of obesity. *Nutr. Diabetes* **2013**, *3*, e68.