Cannabinoids

Cannabis is one of the oldest medicines known to man. Over the last 50 years research has uncovered the endocannabinoid system, a part of our physiology with great therapeutic potential. This article introduces a subject overlooked by medical education.

An old medicine

The earliest writings on cannabis are from China from about 2700BC. It has continued to be broadly used since for a huge variety of medicinal purposes (*Figure 1*) and was often used in combination with other available plant medicines of the time. In the early 1830s research undertaken in India led a doctor, William O'Shaughnessy, to introduce it to the medical profession in the UK. Many subsequent studies were for uses in conditions that are being studied today (*Figure 1*).

However, the advent and success of purified and standardized morphine and aspirin at the end of the 19th century led to a decline in cannabis use. Furthermore the 'reefer madness' campaigns in the USA, combined with political and commercial skulduggery, led to attempts to eliminate the cannabis plant completely. However, its use continued in many countries as a mild anxiolytic, analgesic and hypnotic but fell from favour with the introduction of the benzodiazepines, which were considered modern and safe. In 1971 cannabis was condemned by the UN as having no therapeutic use and, being supposedly highly addictive, it was removed from the pharmacopeia, becoming a schedule 1 substance. Interestingly, in the UK, heroin and cocaine were kept as medicines.

In 1964 Mechoulam in Israel identified Δ9 tetrahydrocannabinol as the psychoactive ingredient, principally obtained from the flowering heads of female plants. It is active at both CB1 and CB2 receptors (*Tables 1* and *2*), and at high doses it produces the effects seen in recreational use.

Earlier in 1940, cannabidiol had been isolated but its effects were unknown. We now know it has potential for the management of anxiety, psychosis, inflammation, nausea and vomiting as well as having neuro-protective and antioxidant properties.

So far a total of 104 cannabinoids and a further 441 non-cannabinoids (e.g. terpenes) have been identified in the plant, some of which provide the characteristic aroma and taste and may have therapeutic effects themselves. Synthetic cannabinoids have also been developed.

Figure 1. Historical examples of cannabis use.

Ancient: Middle East, Asia
Gout, constipation, malaria, rheumatism, menstrual problems, anaesthesia, sleep, decongestion, appetite, soothing, aphrodisiac

19th century UK (hundreds of papers)
Neuralgic pain of arm, sciatica, inflammation of knee, facial neuralgia, rheumatic pain, neuritis, toothache, migraine, dysmenorrhoea (Queen Victoria), anticonvulsant, muscle relaxant, restlessness, anxiety in terminal illness

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Table 1. Physiological effects of cannabinoids

Fine tuning, damping, inhibition
Downregulation of neurons
Inhibit neurotransmitter release
Modulation of neuronal plasticity
Modulation of inflammation
From Di Marzo et al (1998)

Table 2. Principal clinical effects of cannabinoids

Relax (muscles)
Damping pain
Forget (unpleasantness)
Protect (tissues)
Enhancing appetite
Promoting sleep
From Di Marzo et al (1998)

The endocannabinoid system

Fortunately, the basic science of cannabinoids continued to be studied in vitro and in vivo. In 1988 Devane and others identified a G-protein-coupled cannabinoid receptor in the brain, labelled CB1, which was later found to be widespread throughout the body. In 1992 the ligand for CB1, arachidonyl ethanolamide (anandamide), was found.

Soon after, the CB2 receptor was discovered, predominantly in immune system tissues and a further ligand, 2 arachidonyl-glycerol was found. Both ligands are derivatives of arachidonic acid, and broken down by the fatty acid amide hydrolase or monoacylglycerol hydrolases. The discovery was equivalent to that of the endogenous opiate system in the late 1970s. The basis for a huge new area of biological and therapeutic study had been established.

The functions of these components at the synapse provide the basis of the endocannabinoid system. This knowledge opened up the possible importance of endocannabinoids in other biological systems (e.g. immune, gut, urogenital, cardiovascular). The endocannabinoid system is now thought to be more widespread than the endogenous opiate system, explaining the variety of potential therapeutic uses (Pertwee, 2012).

The endocannabinoid system is a very complex system with multiple neurological and immunological roles in the body (Skaper and Di Marzo, 2012). For example, where there is tissue inflammation generating pain, the endocannabinoid system is activated on mast cells, at the peripheral nerve terminal, the dorsal horn of the spinal cord and at most sites processing pain signals up through the CNS to the cortex. Interestingly, CB receptors are sparse in the vital centres in the brainstem which probably explains the complete lack of any deaths recorded in the medical literature directly caused by toxicity from excessive

cannabis consumption. The lethal dose of tetrahydrocannabinol has been estimated as a possible 9 g/kg (in monkeys) which is likely to be the best estimate for a human. Used as a medicine, the current maximum daily dose is 32.4 mg of tetrahydrocannabinol.

Medicinal cannabinoids

In 1985 the first properly developed medicinal cannabinoid was the oral synthetic tetrahydrocannabinol analogue, nabilone, for use in preventing chemotherapy-induced nausea and vomiting. The lack of a parenteral formulation limited its use but it later enabled the early exploration of its use in managing pain and spasticity from multiple sclerosis. Soon after, oral dronabinol, synthetic tetrahydrocannabinol, was produced and used, mainly in the USA. For many patients in the 1990s, these were not as effective as herbal cannabis, either because of the intrinsic nature of the cannabinoid used or because of the method of administration. Illicit cannabis is very variable in its composition which may significantly influence the therapeutic effect.

By the mid-1990s people started to 'come out' about recreational cannabis use and patients began to talk openly about their personal use in the control of pain and spasticity symptoms, predominantly for multiple sclerosis.

In 1997 the British Medical Association, and then the House of Lords in 1998, followed by the Institute of Medicine in the USA, called for formal research into the clinical uses of cannabis. This was initially supported by the UK government who later reneged. However, two major problems had to be resolved: there was no high quality standardized preparation of cannabis, nor a reliable and effective delivery system. Smoking it was not an option for three reasons. First, inhaling cannabis rapidly induces high plasma levels, increasing the risk of psychogenic effects. Second cannabis smoke contains carcinogens like tobacco does. Third we do not prescribe medicines to be burnt and then the smoke inhaled.

The first problem was resolved by the selective cultivation under highly controlled conditions of cloned strains of cannabis plants enabling extraction of high levels of single cannabinoids, e.g. 95% tetrahydrocannabinol and cannabidiol. The second problem related to the fact that cannabinoids are oily substances and not soluble in water (unlike opiates), making oral administration slow and varied. Therefore the sublingual or oro-mucosal route for absorption was chosen and proved acceptable to patients and regulators.

Based on a survey of patients using cannabis for their symptoms, a 1:1 combination of tetrahydrocannabinol:cannabidiol (2.5 mg of each per metered spray into the mouth) was initially chosen for study. Cannabidiol ameliorated the side effects of tetrahydrocannabinol, although it might also have its own intrinsic benefits (Russo and Guy, 2006). The mixture became known as nabiximols (Sativex, GW Pharmaceuticals). A number of other strains has been developed and studied for possible therapies. In Europe pharmaceutical grade plant material is available.

Therapeutic studies and use

Cannabis has a wide range of potential effects and uses (Bab, 2011), but the initial research focus was on spasticity and spasms associated with multiple sclerosis. A number of clinical trials led to formal licensing in 2010 for this indication, based on effectiveness, quality and safety (Novotna et al, 2011). Other studies have looked at the use of cannabis to treat neuropathic pain (Nurmikko et al, 2007), bladder dysfunction in multiple sclerosis, intractable cancer pain and rheumatoid arthritis (Ware and Desroches, 2014). In Canada nabiximols was approved for neuropathic pain in 2005 and then cancer pain in 2007 based on UK research. Patients in these studies have been those most resistant to other therapies, so the most difficult to treat successfully. Nothing else works for them.

Other cannabis extracts have been used for MRC-sponsored studies (e.g. CAMS study, Zajicek et al, 2003) but while positive results were obtained, the materials used were not taken forward as a medicinal product. Nabilone has never been formally taken forward beyond its use to treat chemotherapy-induced nausea and vomiting. Dronabinol has been studied for use to treat chemotherapy-induced nausea and vomiting and for anorexia in AIDS-wasting syndrome.

Clinical use

The patient response to cannabinoids is highly variable and an understanding of the pharmacokinetics and pharmacodynamics is essential. For example vaporization and inhalation can rapidly lead to high peak plasma levels and side effects. The key to use in clinical practice is to titrate the medicine carefully to optimum effect, usually starting at night time. Nabiximols is the easiest in this respect, and a formal schedule has been developed to guide a controlled increase in dose and customisation to the effects. Benefit can be evaluated over 2–3 weeks but multiple useful effects may be seen (*Figure 2*). The onset of the side effects of dizziness or drowsiness are end points that can limit titration, although they may remit over time (Notcutt and Clarke, 2014). Studies of long-term use of nabiximols have shown stability of dosing with rare increases but, more often, a lowering of intake over time (Serpell et al, 2013).

Figure 2. Report from a patient with multiple sclerosis using Sativex. From Notcutt and Clarke (2014).

> 'The fatigue goes. The migraine attacks are reduced; sleep is better. The spasms and cramps are cured, night-time visits to the toilet are less; balance is improved. The strange sensations in the legs are improved; I am able to move and dress more easily.'

Titration with nabilone is much more difficult because of the slow oral route and the unavailability of a range of doses. In Europe pharmaceutical grade standardized cannabis is available (Bedrocan) but administration and titration can be a problem for many patients.

Side effects of medicinal use

For a patient immobilized because of the disease, there is no benefit in being made more immobile by a cannabinoid. With appropriate titration, side effects are minimal and the effects such as euphoria seen with recreational cannabis use are not a problem. Psychotic symptoms are rare and often have other causes (e.g. severe infection). There are no significant interactions with other diseases or medicines. In the medical literature no death has been proven to be directly the result of systemic cannabis toxicity, even with recreational use. Dependency is not a problem and there is no significant withdrawal syndrome with medicinal cannabis (Wang et al, 2008; Robson, 2011; Notcutt et al, 2012).

Driving

Studies in simulators have shown that acute use of cannabis can slow reaction times and can disturb steering around corners. However, this is offset by the driver generally preferring to drive more slowly. These studies mimicked recreational use rather than the much lower levels found with therapeutic doses (Sexton et al, 2000). As with other medicines, it is not illegal to drive while using medicinal cannabis

KEY POINTS

- The endocannabinoid system is ubiquitous and cannabinoid receptors are widespread in the body.
- Multiple sclerosis spasticity responds to cannabinoids.
- Multiple therapeutic effects are not unusual.
- Nabiximols (Sativex) is a purified extract of cannabis.
- In therapeutic use cannabinoids are very safe, and their potential uses are growing rapidly.

providing the patient properly evaluates the effect of the medicine and the underlying medical condition on his/her ability to drive (Department of Transport, 2015).

The medical marijuana user

Some patients may want to discuss their use of illicit plant materials both medicinally and recreationally. Good Medical Practice requires doctors to be prepared to do this and advise on safety in usage. There is a wealth of information on the internet, good and bad, on all aspects from cultivation through to side effects. For the doctor, there is a growing literature advising on medicinal use. While I am prepared to discuss these issues my personal line stops at giving advice on self cultivation and on how to obtain illicit cannabis.

Some emerging uses

Studies are underway in the use of nabiximols for cancer pain. Cannabidiol is in phase 3 trials for intractable childhood epilepsy which is likely to be extended to adults later (Devinsky et al, 2014). Studies are underway as chemotherapy for glioblastoma multiforma and there is evidence for such use against other cancers (Velasco et al, 2014). Cannabinoids are neuro-protective and are being studied for neonatal hypoxia. The potential number of therapeutic possibilities is growing steadily on a background of increasing basic research (e.g. post-traumatic stress disorder, migraine, ulcerative colitis, autism, tetanus, insomnia). Clinical evaluation lags a long way behind.

While there is a link between recreational use of high tetrahydrocannabinol cannabis (skunk) in adolescents and emergence of psychosis, cannabidiol probably protects against this (Degenhardt and Hall, 2002). Study of cannabidiol as an antipsychotic therapy is in progress.

A wider perspective

Politicians still struggle with issues over cannabis. As with opiates, there is a wide variety of legislation and attitudes in different countries. Some now allow the widespread sale of cannabis (even the USA), which may be designated as 'medical cannabis or marijuana'. This is a totally unregulated industry and any such products will not have been formally medically evaluated. Some consider this to be a back door to legalization for recreational use (D'Souza and Ranganathan, 2015).

There has been little comment over National Institute for Health and Care Excellence's (2014) decision to consider nabiximols as not being cost effective. Other economic evaluations have shown the reverse (All Wales Medicines Strategy Group, 2014). Patients who are non-responders only use medicinal cannabinoids for a 4-week evaluation, unlike high cost disease-modifying drugs where long-term benefit can be much harder to assess.

Conclusions

Cannabis sativa has a long history as a safe and useful medicine in many cultures worldwide. This article has outlined the potential for its use in varied forms in many disease processes. The endocannabinoid system has been extensively studied and the opportunities for research are massive as we work to understand it and manipulate it therapeutically. Incorporation of this physiological system into mainstream health education is long overdue. **BJHM**

Conflict of interest: Dr W Notcutt has received fees for consultancy and speaking at meetings. He has taken part in about 20 clinical trials, mostly multicentre for GW Pharmaceuticals and has been the chief investigator on several. His research team has been supported by GW Pharmaceuticals and other pharmaceutical companies.

All Wales Medicines Strategy Group Secretariat Assessment Report (2014) Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®). www.awmsg.org/awmsgonline/app/appraisalinfo/644 (accessed 16 April 2016)

Bab I (2011) Themed issue on cannabinoids in biology and medicine. *Br J Pharmacol* **163**(7): 1327–8 (doi: 10.1111/j.1476-5381.2011.01536.x)

Degenhardt L, Hall W (2002) Cannabis and psychosis. *Curr Psychiatry Rep* **4**: 191–6 (doi: 10.1007/s11920-002-0026-5)

Department of Transport (2015) Guidance for healthcare professionals on drug driving. www.gov.uk/government/uploads/system/uploads/attachment_data/file/325275/healthcare-profs-drug-driving.pdf (accessed 16 April 2016)

Devinsky O, Cilio M, Cross H et al (2014) Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* **55**(6): 791–802 (doi: 10.1111/epi.12631)

Di Marzo D, Melck D, Bisogno T, De Petrocellis L (1998) Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci* **21**(12): 521–8 (doi: 10.1016/S0166-2236(98)01283-1)

D'Souza DC, Ranganathan M (2015) Medical marijuana: is the cart before the horse? *JAMA* **313**(24): 2431–2 (doi: 10.1001/jama.2015.6407)

National Institute for Health and Care Excellence (2014) Multiple sclerosis in adults: management. http://guidance.nice.org.uk/cg186 (accessed 16 April 2016)

Notcutt W, Langford R, Davies P, Ratcliffe S, Potts R (2012) A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols). *Mult Scler* **18**: 219–28 (doi: 10.1177/1352458511419700)

Notcutt W, Clarke E (2014) Cannabinoids in clinical practice: a UK perspective. In: Pertwee R, ed. *Handbook of Cannabis.* Oxford University Press, Oxford: 415–34

Novotna A, Mares J, Ratcliffe S et al (2011) 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* **18**: 1122–31 (doi: 10.1111/j.1468-1331.2010.03328.x)

Nurmikko TJ, Serpell MG, Hoggart B et al (2007) Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* **133**: 210–20 (doi:10.1016/j.pain.2007.08.028)

Pertwee RG (2012) Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. *Philos Trans R Soc Lond B Biol Sci* **367**(1607): 3353–63 (doi: 10.1098/rstb.2011.0381)

Robson P (2011) Abuse potential and psychoactive effects of d-9-tetrahydrocannabinol and Cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. *Expert Opin Drug Saf* **10**: 675–85 (doi: 10.1517/14740338.2011.575778)

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

Serpell M, Notcutt W, Collin C (2013) Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. *J Neurol* **260**: 285–95 (doi: 10.1007/s00415-012-6634-z)

Sexton BF, Tunbridge RJ, Brook-Carter N, Jackson PG, Wright K, Stark MM, Englehart K (2000) The influence of cannabis on driving. TRL Report 477. www.erowid.org/plants/cannabis/cannabis_driving6.pdf (accessed 16 April 2016)

Skaper RD, Di Marzo V (2012) Endocannabinoids in nervous system health and disease: the big picture in a nutshell. *Philos Trans R Soc Lond B Biol Sci* **367**(1607): 3193–200 (doi: 10.1098/rstb.2012.0313)

Velasco G, Sanchez C, Guzman M (2014) Cancer. In: Pertwee R, ed. *Handbook of Cannabis.* Oxford University Press, Oxford: 626–44

Ware M, Desroches J (2014) Medical Cannabis and Pain. IASP Clinical Updates http://iasp.files.cms-plus.com/AM/Images/PCU/PCU_22-3_WEB_final.pdf (accessed 16 April 2016)

Wang T, Collet JP, Shapiro S, Ware MA (2008) Adverse effects of medical cannabinoids: a systematic review. *Can Med Assoc J* **178**: 1669–78 (doi: 10.1503/cmaj.071178)

Zajicek J, Fox P, Sanders H et al (2003) Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* **362**: 1517–26