Do cannabinoid drugs have a therapeutic value as analgesics?

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The medicinal use of cannabinoids in pain relief has been little researched. Reasons include problems caused by legislation, recreational misuse, perceived addictive qualities, and the lack of standardised compounds for administration.

Cannabis still remains an illegal substance for recreational use, despite conflicting reports. Its constituent cannabinoids are also illegal substances. Licensing approval is required from the Home Office to prescribe, possess and supply the drug for medical research.

Research and reports on the clinical use of cannabinoids in pain relief present opposing views, and evidence on their analgesic properties is based strongly on laboratory pain models.

Cannabis was introduced to British medicine as early as 1842 by a British Army surgeon named W.B. O'Shaughnessy (Hall et al, 1994). The first study of cannabis (as opposed to cannabinoids) for pain relief was conducted by Holdcroft et al in 1997. Cannabis-based medicine is a mixture of cannabinoids and other plant materials. A cannabinoid is a single specific compound.

Tetrahydrocannabinol (THC)
The potential of cannabinoids for clinical use has been based on identifying cannabinoid receptors and naturally occurring cannabinoids known as endocannabinoids, which are ubiquitous in the human body. Cannabis sativa plants also produce natural cannabinoids. These are present in the resin, stalks and leaves, flowers and seeds of the plant. The quantity of THC varies, depending on which part of the plant is extracted. For example, cannabis resin secreted by the plant may have a THC content of 10-20%, but hashish oil - the product of extraction by organic solvents - may have a THC content of between 15 and 30% (Ashton, 2001).

The key chemical constituents of cannabis are:
- THC
- Cannabidiol (CBD)
- Cannabinol (CBN).

The percentage of THC, CBD and CBN which can be extracted varies greatly, depending on the
environment in which the plant is grown and how it is processed for medicinal use.

The major psychoactive ingredient of cannabinoids is THC. THC was not accessible as a single compound until 1964 when it was isolated by Goani and Mechoulam.

**Endocannabinoids**

Plant-derived cannabinoids have been used for thousands of years, whereas animal-derived endogenous cannabinoids have only recently been identified. Following the discovery of cannabinoid receptors by Devane et al (1988), the search began for an endogenous ligand with which the receptors interact. According to Ashton (2001): 'Such a substance was isolated from the pig brain by Devane et al (1992) and was found to be chemically different from plant cannabinoids: it is a derivative of the fatty acid arachidonic acid (arachidonyl ethanolamide) related to the prostaglandins. This endogenous substance was named anandamide.'

Endocannabinoids are formulated within neural and other tissues. They act in a similar fashion to other neuromodulators, in that they are released after stimulation, activate specific receptors, and undergo rapid uptake and degradation (Vaughan and Christie, 2000). They can either dampen or enhance neural cell excitation.

**Cannabinoid receptors**

At least two distinct human cannabinoid transmembrane receptors have been discovered and cloned, namely CB1 and CB2. The cannabinoid receptor CB1 was identified by Devane et al (1988) and can be identified in central neuronal tissues and in peripheral nerves. CB2 receptors, discovered by Munro et al (1993), can be identified in macrophages in the spleen, in reproductive tissues and are also identifiable in other immune tissues within the body (Vaughan and Christie, 2000).

The location of the CB1 receptors at the central nervous system offers a degree of understanding and insight into both the pain-relieving properties and side-effects that people experience. CB1 receptors can be found in the areas of the brain that control mood, motor control, formation of memory, regulation of food intake, autonomic control and the processing of painful or noxious stimuli, and in peripheral autonomic and reproductive tissues. In the peripheral tissues, cannabinoid agonists may produce analgesia by acting on both CB1 and CB2 receptors.

The discovery of CB1 and CB2 receptors is a major advance for cannabinoid research because there is a possibility that in the future plant-derived or man-made agents could potentially be designed to work on molecular targets and also on specific physiological mechanisms.

Although only two cannabinoid receptor sites have so far been located, more receptor sites may yet be discovered.

Other sites of action may be relevant, for example vanilloid and opioid receptors may also be involved in cannabinoid physiology.

**Therapeutic properties**

Substantial basic science and laboratory evidence suggests that cannabinoids, either plant-derived, synthetic or endogenous, may hold a degree of therapeutic potential in the management of pain. Clinical evidence to support this theory is now accumulating. 'Small clinical trials have demonstrated analgesic potential in acute and chronic pain,' found Holdcroft and Patel (2001) in an expert pain review. 'The results of large clinical trials into cannabinoid use for acute pain are expected to be a catalyst for wider studies and possible changes in legislation.'

The main effects produced by cannabis, when used for recreation, usually occur from smoking and inhaling toxic doses. They include perceptual alterations or a 'high'. Anecdotal evidence also exists to suggest that cannabinoids have significant analgesic properties.

In the 19th century British army surgeon W.B. O'Shaughnessy advocated its use as an anti-spasmodic, anti-emetic, anti-convulsant and above all its use in pain relief in tetanus, rheumatism and epilepsy (Hall et al, 1994).

In Holdcroft et al's first study (1997) of the use of cannabis for pain relief, she discovered that cannabis reduced morphine requirements in familial Mediterranean fever and had the potential to act as an analgesic. The euphoriant effect is thought to be induced with smoked doses of THC as low as 2.5mg (Ashton, 2001).

Clearly it is very difficult to ascertain the amount of THC one would receive via smoking because of the lack of standardisation, unless additional products from the natural cannabis plant were added to enhance its effects, for example increasing the amount of cannabis oil in the smoked joint.
Only a few human experimental studies have reported evidence of an analgesic effect. One double-blind trial, conducted by Noyes et al (1975), compared the analgesic efficacy of oral THC and codeine in patients with cancer pain. The findings suggested that 20mg of THC produced the same level of analgesia to that of 120mg of codeine.

An abundance of laboratory evidence supports claims for cannabinoid pain-relieving properties in conditions such as multiple sclerosis and familial Mediterranean fever. However, it is not enough to draw sound scientific conclusions from this alone, as so few participants are involved in the studies. Further clinical research is necessary to back these theories.

Comparison with existing conventional analgesics
'There is some support obtained from animal studies that THC has an analgesic effect which operates via a different mechanism from that of the opioid drugs,' according to Segal (1986).

This line of investigation has spawned great interest in the realm of pain management. In any opioid, the potential exists for dependence to occur. If this can be avoided with cannabinoids, the drug seems set to become all the more attractive for use in analgesia. But Ashton (2001) disagrees. He suggests that effects cannabinoids produce can be reversed by naloxone, thus reinforcing the probability of an opioid link.

Hamann and Di Vadi (1999) tested this in a clinical setting by administering naxolone, an opioid receptor antagonist, to a patient who was in pain and had previously received nabilone, a synthetic cannabinoid, for pain relief. Intravenous injections of naloxone did not reverse the patient's pain relief. These clinical findings disprove Ashton's hypothesis and suggest that cannabinoid analgesia is mediated independently of the opiate pathway (Hamann and Di Vadi, 1999).

Clearly further pharmacokinetic investigation is required before cannabinoids can be considered as an analgesic of choice. At this point the question arises, how many adverse effects does a person have to experience in order to experience a clinically beneficial analgesic effect?

Only more pharmacological research and standardised material to administer to patients will enable us to answer this.

Adverse effects
The psychoactive effects of THC exploited by recreational users - the euphoriant effect and relaxed states - have been most unwelcome to cannabis-naïve people, and are often reported as reasons for reducing or ending use.

Reported dysphoric side-effects of THC include severe anxiety, paranoia, panic reactions and perceptual alterations. Many people find them disagreeable and cease use. CBD is known to mitigate these effects.

As with all drugs, a serious risk of adverse effects is posed with the use of cannabinoids. However, Weil (1988) says: 'The most common psychoactive effects of cannabis are minor and non-life threatening and self-limiting effects that can be easily managed, and are of much less severity than the side-effects of many other widely used therapeutic drugs.'

Cannabinoids have been found to produce adverse cardiovascular effects. Tachycardia, postural hypotension and syncope attacks have all been reported. Ultimately this would not be the analgesic of choice for those who have ischaemic heart conditions, due to the potential of myocardial infarction.

Ashton (2001) highlights the potential for increased risk for users who have pre-existing cardiac disease, and reports on several cases of acute and sometimes fatal cardiac incidents in young smokers.

However, it is worth pointing out that fatal cardiac incidents can occur in young smokers at any point as a result of inhaled nicotine, without the addition of THC. There are no confirmed published cases worldwide of human deaths from cannabis poisoning, argue Hall and Solowij (1998).

Current clinical trials
A Medical Research Council study designed to establish the analgesic efficacy of cannabinoids on acute postoperative pain, designed by Dr Anita Holdcroft, reader in anaesthesia at Imperial College, and honorary consultant anaesthetist at Chelsea and Westminster Hospital, is being conducted at London's Imperial College of Medicine. A second MRC study, devised by Dr J. Zajicek, a consultant neurologist at Derriford Hospital, Plymouth, is under way to establish the therapeutic potential of cannabinoids as analgesia in multiple sclerosis, by comparing the effect of three different treatments on muscle spasticity in patients with MS.

It is hoped that these trials will act as a benchmark for future practice and clinical use and perhaps help to quash the current resistance into research of cannabinoids.
Conclusion
Some convincing experimental evidence exists, though limited, to suggest cannabinoids have therapeutic value. The need has grown for further well-designed and controlled clinical trials, to uncover cannabis's true therapeutic potential. When the full clinical benefits and side-effects are uncovered, and a standardised preparation is available, the possibility is strong that cannabinoids will positively contribute to the management of a patient's pain.

Glossary of terms
CB1: A cannabinoid receptor located in central neuronal tissues and in peripheral nerves
CB2: A cannabinoid receptor located in reproductive and immune tissues
Cannabinol (CBN): A plant-derived cannabinoid
Cannabidiol (CBD): A plant-derived cannabinoid
Endogenous: Naturally occurring within the human body
Ligand: A substance acting at a receptor site.
Tetrahydrocannabinol (THC): The principal active cannabinoid found in cannabis

Further reading

Noyes, R. Jr, Brunk, S.F., Avery, D.A., Cater, A.C. (1975) The analgesic properties of delta-
9-tetrahydrocannabinol and codeine. Clinical Pharmacology and Therapeutics 81: 1, 84-89.


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