# Cannabis and cannabis-based medicines: potential benefits and risks to health

Martin R Wilkins, on behalf of the Working Party on Cannabis and Cannabis-based Medicines

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Cannabis or marijuana from the plant *Cannabis sativa* has been used for centuries in India and the Middle East as an intoxicant and medicine. A young Irish doctor, William O'Shaugnessy, who served in the East India Company, first brought cannabis to Britain in 1842.[1] Subsequent reports appeared in British medical journals describing its application in a variety of conditions, including menstrual cramps, asthma, childbirth, quinsy, cough, insomnia, migraine headaches, and even in the treatment of withdrawal from opium.[2] After an enthusiastic welcome by physicians in the nineteenth century, medicinal cannabis fell out of favour in the twentieth century. The imported herbal cannabis was of variable quality and potency, and new and more reliable medicines began to replace it. Tincture of cannabis finally left the *British Pharmacopoeia* in 1973.

At present, concerns about the health risks of cannabis, particularly the risk of psychosis, of dependence and the possibility that it might be a gateway to the use of more potent drugs such as cocaine, means that its production, supply and possession is illegal in many countries. Nonetheless, it is still the most commonly used recreational drug in the UK (used by 27% of the adult population during their lifetime, by 9% in the past year and 6% in the past month) and thousands of patients with AIDS, multiple sclerosis, chronic pain and a variety of other disabling diseases have tried and continue to use cannabis in the firm belief that it makes their symptoms better. These positions illustrate the extremes of public opinion, so that while some highlight the dangers of cannabis, others feel that patients are being deprived of a useful medicine for conditions that are poorly served by currently available therapeutic agents.

Against this background, the Royal College of Physicians established a working party 'to assess the health consequences of cannabis use in order to clarify the benefits and risks of using cannabis and its derivatives for medical purposes'. Following its Terms of Reference, the Cannabis Working Party focused on the scientific case for cannabis and cannabis-based medicines, rather than on moral issues or its legal status. The Working Party held a series of meetings to consider written and oral presentations from experts from academia, practising physicians, the pharmaceutical industry, regulatory agencies and patient representatives during the period October 2004 to June 2005 and has now published a report of its findings and recommendations.[3]

## Cannabis preparations

Most people who use cannabis illicitly smoke dried flowers, leaves or extracts from the plant in a hand-rolled cigarette (joint) or in a water pipe (bong). The effects of this are experienced within minutes but the smoke contains many of the substances considered to be harmful in tobacco smoke. This gives concern that taking cannabis in this manner carries the same risks to the lung as smoking tobacco and so is strongly discouraged.

There are alternative and more acceptable routes of cannabis administration. Oral preparations of THC ($\Delta^9$-tetrahydrocannabinol), the main psychoactive ingredient of cannabis, include synthetic THC known as dronabinol (or Marinol®) and a synthetic analogue of THC, called nabilone (or Cesamet®). Unfortunately, the bioavailability of THC or cannabis extract after oral ingestion is poor and varies considerably between individuals. A herbal extract delivered as a mouth spray (Sativex®) achieves more effective and reproducible absorption and is currently being evaluated in a number of clinical trials.

## Medical indications

Currently, there are two recognised medical indications for THC: the treatment of chemotherapy-induced nausea and vomiting in patients who have failed to respond adequately to conventional anti-emetic treatments, and the treatment of AIDS-related wasting syndrome. Dronabinol has approval from the Food and Drugs Administration for both indications in the USA, while nabilone has approval as an anti-emetic in cancer patients in both the USA and the UK. Dronabinol does not have a product licence in the UK but can be imported and prescribed on a named patient basis. The use of these

cannabis-based preparations in chemotherapy has been overshadowed by the emergence of new effective anti-emetic agents in recent years.

Two medical indications for which approval has been sought are the treatment of multiple sclerosis and the management of chronic pain. Both are medical conditions in need of more effective therapies. Placebo-controlled, randomised clinical trials of dronabinol and Sativex® have provided some evidence that these drugs reduce spasticity and neuropathic pain and improve sleep quality in patients with multiple sclerosis, and may have an effect on the course of the disease.[4,5] There are data to suggest that cannabis may be of benefit in other causes of neuropathic pain.[6,7] But the results to date are not conclusive. Sativex® has been granted a conditional licence in Canada for the treatment of symptomatic neuropathic pain in patients with multiple sclerosis, and the Home Office has granted permission for the drug to be imported into the UK for prescription by doctors for the same indication on a named patient basis. Further carefully controlled clinical trials with these formulations evaluating their efficacy in the treatment of the symptoms of multiple sclerosis and chronic pain are still required and indeed are already underway.

Currently, there are no controlled clinical trial data to support the use of cannabis for other medical conditions.

## Safety

The safety profile of THC as a compound is good insofar as high doses are rarely, if ever, lethal. However, there is a narrow dosing window between the desired and undesired effects, which varies between individuals, in part depending upon previous exposure to the drug. Recognised undesired effects include unpleasant psychological reactions, intoxication and temporary impairment of skilled motor and cognitive functions. The practice of allowing patients to self-titrate their dose against symptoms can help to circumnavigate these problems and does not result in escalating doses.

Major concerns arising from studies of the recreational use of cannabis are the risk of developing a long-term mental illness, the risk of becoming dependent on the drug and the possibility that it may lead on to other stronger drugs. Epidemiological studies show that there is an association between regular cannabis use in adolescence and subsequent psychosis or psychotic symptoms.[8,9] It is not clear from these reports that regular cannabis use actually causes mental illness but the association raises an alarm. Cannabis and cannabis-based medicines should not be given to adolescents or people with a history of severe mental illness unless there are clear benefits from such medicines in such individuals and even then careful observation of these patients is necessary.

Studies of regular users of cannabis for recreational purposes suggest that around 10% show evidence of dependence.[10] On the other hand, studies of the use of THC and cannabis extracts in multiple sclerosis for up to 12 months have not reported dependence on the drug as a problem, even though patients were allowed to vary the dose they used themselves to achieve the benefit desired. Similarly, there is no evidence that the use of THC and cannabis extracts in clinical trials leads to the use of stronger medicines, such as opiates. Likewise, the incidence of psychotic symptoms is low in these clinical trials.

## The endogenous cannabinoid system

Cannabis exerts its effects through two distinct receptors, $CB_1$ and $CB_2$. The $CB_1$ receptor subtype is found in the brain while the $CB_2$ subtype is found in peripheral tissues, principally those of the immune system. In recent years, it has become clear that the body produces its own cannabis-like substances (endocannabinoids) that act on these receptors. The physiological roles of these substances are gradually being defined, and include the regulation of appetite and factors which might influence cardiovascular disease and bone strength. This raises the interesting possibility in the near future of new drugs for the treatment of obesity, heart disease and osteoporosis. Ultimately, the benefits and safety of these drugs have to be evaluated in studies designed according to well laid out regulatory guidelines for the development and approval of new medicines.

## Members of the Working Party

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