Medical uses of marijuana (*Cannabis sativa*): fact or fallacy?

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ABSTRACT

Marijuana (*Cannabis sativa*) has been used throughout the world medically, recreationally and spiritually for thousands of years. In South Africa, from the mid-19th century to the 1920s, practitioners prescribed it for a multitude of conditions. In 1928 it was classified as a Schedule I substance, illegal, and without medical value. Ironically, with this prohibition, cannabis became the most widely used illicit recreational drug, not only in South Africa, but worldwide. Cannabis is generally regarded as enjoyable and relaxing without the addictive risks of opioids or stimulants. In alternative medicine circles it has never lost its appeal. To date 23 States in the USA have legalised its medical use despite the federal ban. Unfortunately, little about cannabis is not without controversy. Its main active ingredient, δ-9-tetrahydrocannabinol (THC), was not isolated until 1964, and it was not until the 1990s that the far-reaching modulatory activities of the endocannabinoid system in the human body was studied. This system's elucidation raises the possibility of many promising pharmaceutical applications, even as restrictions show no sign of abating. Recreational use of cannabis continues to increase, despite growing evidence of its addictive potential, particularly in the young. Public approval drives medical cannabis legalisation efforts without the scientific data normally required to justify a new medication's introduction. This review explores these controversies and whether cannabis is a panacea, a scourge, or both.

KEY WORDS: Cannabis.
Endocannabinoid.
Marijuana.

Introduction

Marijuana (*Cannabis sativa*; cannabis) is one of the most ancient of psychotropic drugs. Public opinion concerning the drug is contentious and on the questions of the drug and its derivatives, the cannabinoids, being used in medicine, it is sharply divergent. Many dismiss medical cannabis as a hoax that exploits our inborn compassion for the sick, while others will claim it is a distinctively soothing medicine that is being withheld from patients.

Cannabis has been used as a medicine for thousands of years.[1,13–17] The Chinese compendium of herbal medicines, the *Pents'ao*, first published around 2800 BC, recommended cannabis for the treatment of constipation, gout, malaria, menstrual problems and rheumatism. The use of cannabis (dagga as it is known in South Africa) dates back to the 15th century AD, with the first legislation of the drug being introduced in 1928.[18]

Historically, throughout the whole of Southern Africa the 'controlled' use and consumption of cannabis among the African populations was rather pervasive.[19] For example, the use of cannabis was an integral part of the culture of the more traditional (rural) communities and its availability was strictly controlled by tribal elders. The use of cannabis SA and elsewhere in the world has now become the realm of the younger user and by inference also the multidrug user.

Scientific data on provocative subjects are often misinterpreted, over-interpreted or misrepresented and the use of cannabis in medicine is no exception. However, modern medicine must adhere to certain standards of quality and safety from those used in the past. Can cannabis relieve health problems? Is it safe for medical use? The answers to these questions is not whether or not cannabis can be used as a herbal remedy, but rather how well this 'remedy' meets today's standards of efficacy and safety; all major issues of concern.

Society expects all licensed medications to be safe, reliable and of proven efficacy; contaminants and inconsistent ingredients in our health treatments are not acceptable. This also applies to prescriptions, over-the-counter medications as well as vitamins, supplements, herbal and homeopathic remedies purchased from the pharmacy. An example is thalidomide, which was a commonly used drug in the late 1950s and early 1960s for the treatment of morning sickness in pregnant women.

It became evident in the 1960s that thalidomide treatment resulted in severe birth defects. Other effects later ascribed to thalidomide include congenital heart disease, malformations of the inner and outer ear, and visual abnormalities.[20,21]

Although the use of thalidomide was forbidden in the majority of countries,[22] the thalidomide tragedy was a turning point in toxicity testing, as it prompted the US and international regulatory agencies to develop regular toxicity testing protocols.[23] Interestingly, the use of thalidomide as a tool in developmental biology has also led to important discoveries in the biochemical pathways of limb development and ongoing research.

The many disputes concerning the non-medical use of cannabis overflow into the medical cannabis debate and tend to obscure the real state of scientific knowledge.

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The debate over the supposed medical benefits of cannabis remains extremely contentious.

Laws remain controversial in that one of the arguments against the legalisation of medical cannabis is that it is an excuse for recreational cannabis use, which could have a serious negative impact, especially on the youth.[24–28] To date, 23 US States have legalised medical cannabis (Table 1).[5]

Overall, the annual prevalence of cannabis use worldwide has remained, percentage-wise at least, statistically static. Presently, cannabis remains the most widely used illicit substance throughout the world, with an estimated annual incidence in 2010 of 2.6–5.0% of the adult population (i.e., 119–224 million users aged between 15 and 64 years). The highest incidence of cannabis use was reported in Oceania, (predominantly Australia and New Zealand) at 9.1–14.6%, followed by the US at 10.8%, Western and Central Europe at 7.0% and West, Central and South Africa at 5.2–13.5%. The incidence of cannabis users in Asia is 1.0–3.4% and, although lower than the global average, the absolute number of users is estimated between 26–92 million, making it the highest worldwide.[43]

Marijuana and medicine

Cannabis plants have been cultivated and used for thousands of years for herbal use and medications, as well as for its euphoric mood-altering effects. Historical documents are the main source of readily available information on the use of medical cannabis as well as personal accounts of individuals who have used the drug to relieve their medical symptoms. It was not until the mid-19th century that Western medicine 'discovered' cannabis as a medicinal compound.[1]

The current debate over the medical use of cannabis is fundamentally a debate over the value of its medicinal properties compared to the risks posed by its continual use. To date, there are over 20,000 published studies, reviews or clinical trials in the scientific literature. Nearly half of these were published within the last five years.[29–34] This is in sharp contrast to a decade ago where a review of literature on the efficacy, status and overall safety of cannabis and its cannabinoids for pain and spasticity, revealed only nine randomised studies of acceptable quality had been carried out.[35,36]

The understanding of medical risks is also much more apparent today than in previous generations. There are very few herbal medicines that meet these stringent standards even though they have provided the very core for modern Western pharmaceuticals. In fact, most of the current prescriptions have their roots either directly or indirectly in plant remedies.[37] Although many plants continue to be a valuable resource, drug development via the major pharmaceutical companies is less likely to be reliant on plants and more reliant on the means of modern science.

Molecular biology, bioinformatics software, DNA array analysis of genes and analytical chemistry are all beginning to yield results. Recent interest in the medical uses of cannabis coincides with the trend towards 'self-help' and the search for 'natural' and homeopathic therapies and remedies (Table 2).[38-41] It must be borne in mind, however, that few of these alternative therapies have been fully tested for efficacy and safety, as required for all medications as approved by the US Food and Drug Administration (FDA), for example.[11,12,42]

Table 1. US States that permit use of cannabis for certain medical conditions.

• Alaska (AK)	• Illinois (IL)	• New Jersey (NJ)
• Arizona (AZ)	• Maine (ME)	• New Mexico (NM)
• California (CA)	• Maryland (MD)	• New York
• Colorado (CO)	• Michigan (MI)	• Oregon (OR)
• Connecticut (CT)	• Minnesota	• Rhode Island (RI)
• Delaware (DE)	• Montana (MT)	• Vermont (VT)
• District of Columbia (DC)	• Nevada (NV)	• Washington (WA)
• Hawaii (HI)	• New Hampshire (NH)	

Table 2. CAM therapies in the 2007 US National Health Interview Survey (NHIS). An asterisk (*) indicates a practitioner-based therapy.[38]

• Acupuncture*
• Ayurveda*
• Biofeedback*
• Chelation therapy*
• Chiropractic or osteopathicmanipulation*
• Deep breathing exercises
• Diet-based therapies
• Energy healing therapy/Reiki*
• Guided imagery
• Homeopathic treatment
• Hypnosis*
• Massage*
• Meditation
• Movement therapies
• Natural products (non-vitamin and non-mineral, such as herbs and other products from plants, enzymes etc.)
• Naturopathy*
• Progressive relaxation
• QI gong
• Tai chi
• Traditional healers*
• Yoga

Medical value of cannabis and its related substances

Studies on smoked cannabis

The Institute of Medicine (IOM) has received reports in excess of 30 different medical uses of cannabis, and more uses are reported elsewhere in the literature (Fig. 1, Table 3).[44–47] It has to be stressed that cannabis is not a totally benign substance and smoking it long-term is associated with a multitude of health risks. It is recommended, therefore, that smoked cannabis should not be used for

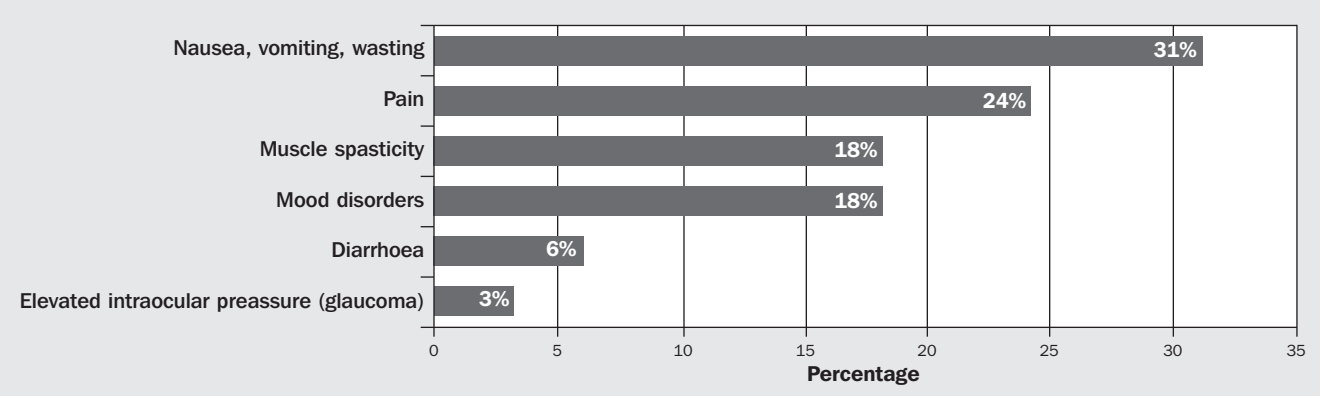

Fig. 1. Reported medical uses of cannabis. Frequency of symptoms among a group of 43 patients who spoke at the IOM public workshops. Twenty of these patients reported using cannabis to relieve more than one symptom.[46,47]

long-term medical use.[46] For certain patients, such as the terminally ill or those with severe debilitating symptoms, the long-term risks of smoking cannabis become somewhat irrelevant.

The ever-increasing advances in understanding the mode of action of tetrahydrocannabinol (THC) and the related cannabinoid constituents of cannabis and the many anecdotal reports on the potential medical benefits have hastened increased research into this rather controversial subject. In the past decade, the extent and rigour of the research into medical cannabis and its various uses has increased dramatically.[47] This ongoing research has employed cannabis, cannabis-based extracts and the use of synthetic cannabinoids using various routes of administration (e.g., smoking, vapourisation, oral, sublingual and mucosal).[48]

There is little doubt that smoking cannabis provides the most rapid and efficient delivery of THC, the primary psychoactive ingredient and most abundant cannabinoid, to the brain. It can be detected immediately in plasma, with peak concentrations occurring within 10 minutes, then decreasing to approximately 60% of peak by 15 minutes, and 20% of peak by 30 minutes. However, there can be wide inter-individual variation in the concentrations achieved.[49]

At present, the clear weight of evidence is that smoking cannabis long-term is harmful. No matter what medical condition has been studied, other drugs already approved by the FDA have been proven to be safer than smoking cannabis long-term. Today, despite legal, social and health risks associated with smoking cannabis long-term, it is still extensively used by particular patient groups.

Chronic pain

Investigations into the short-term efficacy of smoked cannabis for neuropathic pain were conducted in a series of randomised clinical trials. Sponsorship of these trials was by the State of California Medical Marijuana Research Act, promulgated in 1999 and undertaken under the umbrellas of the Department of Health and Human Services, the National Institute of Drug Abuse, California Centre for Medicinal Cannabis Research (CMCR) and the FDA.[10–12,29,45] This assigned participants to smoke cannabis cigarettes containing THC by weight (4–32 mg) or placebo cigarettes from which the THC had been removed.

Two trials enrolled patients who were exhibiting painful human immunodeficiency virus (HIV) peripheral neuropathy;[29,30] one consisted of mixed neuropathic pain due to peripheral or central dysfunction of the nervous system (i.e., complex regional pain syndrome, peripheral neuropathy and traumatic focal nerve or spinal cord injury).[31] All patients continued taking their usual regimen of analgesics while participating in the studies.

The results consistently demonstrated that cannabis significantly reduced pain intensity, with patients reporting a 34–40% reduction in pain on cannabis compared to 17–20% on the placebo. Interestingly, a greater proportion of patients reported at least a 30% reduction in their overall pain on cannabis (46–52%) compared to those on the

Table 3. Other reported uses of cannabis.[46,47]

•ALS	•Glaucoma	•Multiple sclerosis
•Alzheimer's	•Hepatitis C	•Osteoporosis
•Diabetes	•HIV	•Pruritus
•Dystonia	•Hypertension	•RA
•Fibromyalgia	•Incontinence	•Sleep apnoea
•GI disorders	•MRSA	•Tourette's syndrome

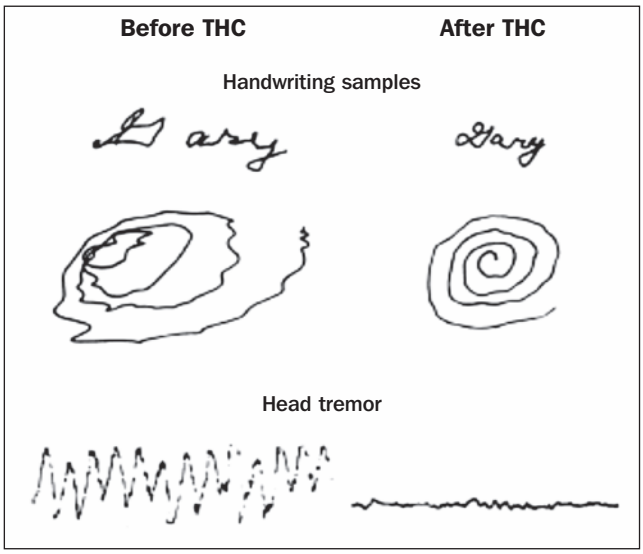

Fig. 2. Effect of THC on tremor caused by MS. Adapted and reprinted by kind permission (Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. *Ann Neurol* 1983; **13** [6]: 669–71).

placebo (18–24%).[29–31] These figures are extremely relevant in that an overall 30% reduction in pain intensity is commonly associated with an improved quality of life.[32] This 30% reduction is also in the range achieved by prescribed standard non-opioid drugs such as noradrenergic antidepressants and anticonvulsants. Of interest was that medium-dose cannabis cigarettes (3.5% THC) were as effective as those containing the higher dose (7% THC).[31]

Effects of THCs on the spasticity seen in the majority of multiple sclerosis (MS) patients was tested in three separate clinical studies, which together controlled a total of 30 MS patients.[49–52] All three were open trials in which all participants knew that they would be receiving THC. The results were in some cases quite dramatic, with most patients reporting markedly improved symptoms (Fig. 2). However, THC was not effective for all patients and in some instances caused unpleasant side-effects.

Studies of oral preparations

The two main oral preparations are synthetic THC (dronabinol, Marinol) and its synthetic analogue (nabilone, Cesamet). The major disadvantage of using such products is that the absorption from the intestine is slower and hence a belated plasma peak concentration is exhibited, as compared to that seen with the short-term smoking of cannabis. The bioavailability range is 5–20% of dose, with peak concentrations occurring one to six hours after ingestion, with a magnitude of approximately 10% of that achieved with short-term smoking.[46,48]

Chronic pain

The majority of the research using oral preparations has focused on neuropathic pain and the spasticity associated with MS. These randomised trials imply that dronabinol (up to 25 mg daily) significantly reduces pain compared to the placebo. The results demonstrated a 50% 'improvement' for those participants on dronabinol compared to 30% on the placebo ($P<0.05$).[52] The number-needed-to-treat for this 50% pain reduction was 3.5, which is again in the range of the efficacy for the standard prescribed non-opioids.[53] Although the effects on spasticity are varied (i.e., there may be no observable change in examined muscle tone) many patients reported significant relief from their pain.[52] To date there is less research with nabilone, although in one three-week randomised crossover study it was reported that nabilone (2 mg daily) provided modest analgesia compared to dihydrocodeine (240 mg daily) in neuropathic pain.[54]

Nausea-vomiting (emesis) and appetite stimulation

The mainstays for treatment of nausea and vomiting are serotonin receptor (5-HT3) antagonists and Substance P/neurokinin-1 (NK-1) receptor antagonists. Dronabinol and nabilone are also approved for the control of acute and often delayed nausea and vomiting due to, for example, cancer treatment involving chemotherapy.

Studies have indicated that these cannabinoids are as effective, or even more effective in some cases, than the standard drugs such as metoclopramide and the neuroleptics, but their side-effect profile is less favourable in terms of sedation, dizziness, dysphoria, hypotension and anxiety.[55,56] To date, there are no direct comparisons of the cannabinoids with serotonin 5-HT3 receptor or Substance P/NK-1 receptor antagonists.

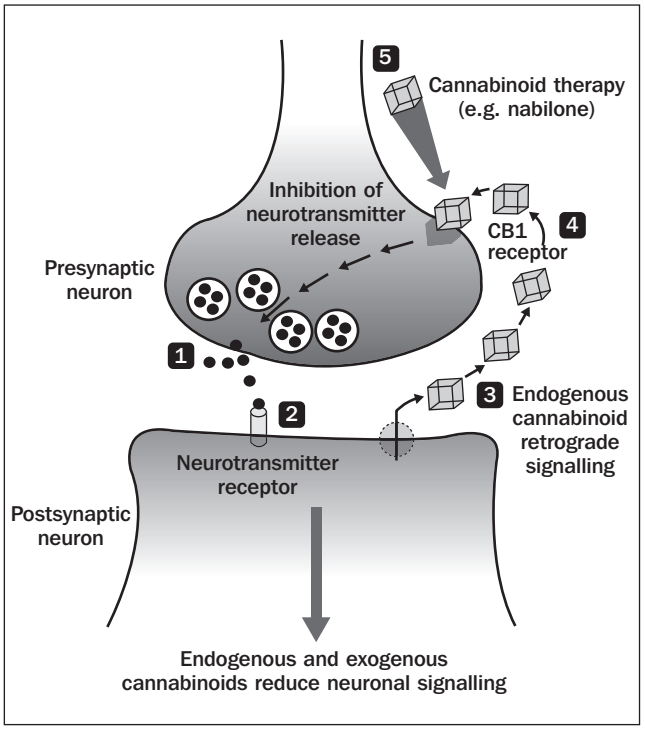

Fig. 3. Mechanism of action of the cannabinoids.[61] Endogenous cannabinoids: response to overstimulation of post-synaptic nerves. Exogenous cannabinoids mimic these effects of inhibition of the presynaptic nerves. CB: cannabinoid.

There are very few effective treatments for anorexia, early satiety, weight loss and cachexia, which are frequent in late-stage cancers and in acquired immunodeficiency syndrome (AIDS). Trials of the effectiveness of dronabinol (5 mg daily) in treating AIDS patients with clinically significant weight loss indicated that it outperformed the placebo in terms of short-term appetite enhancement (38% *vs.* 8% at six weeks). More importantly, these effects persisted for up to 12 months,[57,58] but were not accompanied by differences in weight gain. This could be attributed to disease-associated energy wasting. Unfortunately, the accompanying psychoactive side-effects and the problems of oral administration (e.g., delayed onset of action, variable absorption and extended duration of effect) were all found to be major practical limitations of dronabinol.

Cannabinoid receptors

Cannabinoid receptors of the CB_1 type are present throughout the central nervous system. The largest populations of CB1 receptors, however, are found in parts of the brain that control movement, memory, response to stress and complex thought, functions that are, coincidentally, affected by cannabis.

Research indicates that the body's own cannabinoids play an essential role in all these processes, as well as in pain perception and the control of nausea and vomiting.[59] CB_2 receptors were originally thought to be localised

exclusively in the periphery, primarily on immunocytes and mast cells. However, recent evidence suggests that CB2 receptors are also present on brainstem neurons and as such may have a role in mediating the cannabinoid effects on vomiting.[60]

In a study in 2004,[61] on the mechanisms of action of cannabinoids on wasting syndrome, vomiting and pain, investigators found that, whether through the CB1 receptor agonism alone or combined with CB2 binding, cannabinoids directly and/or indirectly affect serotonin, neurokinin, dopamine and opioid activity. All of these neurotransmitters play a critical role in mediating the emetogenic response to toxins.

Historically, the cannabinoids have been used for their anti-anxiety and distress-relieving effects, and, although limbic system modulation of central processing may be less important for vomiting than for nausea, such activity may be linked to pre-emptive and even delayed CINV.[62–64]

Cannabinoids appear to exert their effects at the cellular level through the presynaptic inhibition of neurotransmitter release, either from the enterochromaffin cells or the central vagal afferents in the dorsal vagal complex (Fig. 3).[61]

Studies on extracts of cannabis

Oral cannabis extracts (Cannador) have been used for clinical trials in Germany. They consist of capsules containing cannabis extract standardised to contain THC and the non-psychoactive plant cannabidiol (2:1 ratio).

Several small- to medium-sized, randomised, controlled trials in patients with MS using daily doses of THC in the range 7.5–27.5 mg[53,65,66] suggest improvements in perceived spasticity and pain. In other trials conducted,[67] but not all,[53,68] observer-assessed spasticity also improved. As yet, Cannador has not been licensed anywhere in the world.[69]

Alternative delivery systems

As mentioned previously, the hazards of smoking cannabis long-term and the pharmacokinetic limitations of ingestion of its cannabinoids has steered investigators in the direction of alternative delivery systems. One alternative is devices that vapourise the cannabis leaves and its flower-tops by heating them to just below the temperature of combustion (i.e., 175–225°C). This permits inhalation of the volatilised gases minus the hazardous pyrroles that are produced by burning. Vapourisation is by no means the perfect solution as carbon monoxide (CO), although at lower levels than that encountered in smoking the drug, is still produced.[70] The CMCR is currently conducting clinical trials to assess the efficacy of vapourised cannabis as an analgesic in chronic neuropathic pain.

The use of sublingual systems of whole cannabis plant extract, employing metered spray devices to deliver measure doses of THC and cannabidiol are undergoing phase 11B/111 trials in the USA. These systems are already licensed elsewhere for cancer pain and MS-associated neuropathic pain and spasticity (i.e., nabiximols, Sativex). In some placebo-controlled trials, it is suggested that there is significant analgesia in neuropathic pain due to MS,[71] and also in mixed neuropathy (e.g., post-herpetic, traumatic, vascular neuropathies).[72]

Conclusions

Cannabis has been demonised, glorified and now increasingly medicalised. The classification of cannabis as a Schedule I drug, as well as the continuing controversy as to whether or not it has any medical value,[73] are barriers to medical progression regarding this rather emotive subject.

There can be no doubt that medical cannabis laws in the USA have challenged the way medical practitioners practice medicine in recommending this Schedule I drug to their patients. Clearly, it is not accurate to say that cannabis has no medical value or that information on safety is lacking,[45,73–78] and although cannabis has some abuse potential, its profile more closely resembles drugs in the Schedule III category, where codeine and dronabinol are listed.

The potential longer-term effects of, and harm caused by, the cannabinoids are as yet not fully understood. These include ongoing abuse and a dependence syndrome, adverse psychiatric and medical effects in those vulnerable populations, and well documented risk to motor vehicle safety when combined with alcohol.[79]

There is a definite need for further studies to assess whether or not cannabis is as effective as the more standard treatments for various diseases, including life-threatening cancers. There is no doubt that the development of innovative modulators of the endocannabinoid system, which may be prescribed and used as more traditional medicines, require further study.

The ongoing debate between scientific evidence for medicinal cannabis and political ideology will hopefully be resolved sooner rather than later, in a judicious manner both in South Africa and the rest of the world.[3,80,81] □

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