

Medical marijuana: A panacea or scourge

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ABSTRACT

Marijuana (*Cannabis sativa*) has been used for recreational and medical purposes since ages. Marijuana smoking is an evil, which is on the rise with about 180.6 million active users worldwide. The recent legalization of marijuana in Uruguay has generated global interest. The purpose of this short review is to describe the various preparations, uses and adverse effects of medical marijuana. It also deals with the adverse effects of marijuana smoking when used for recreational purposes. Based on the current literature, medical use of marijuana is justified in certain conditions as an alternative therapy.

KEY WORDS: Cannabis, marijuana smoking, medical marijuana

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The Brazilian psychopharmacologist E. A. Carlini has aptly said, "Very few drugs, if at all, have such a tangled history as a medicine. In fact, prejudice, superstition, emotionalism, and even ideology have managed to lead cannabis to ups and downs concerning both its therapeutic properties and its toxicological and dependence-inducing effects."^[1]

As Uruguay prepares to become the first country to legalize its illegal market of marijuana, scientifically named as *Cannabis sativa*; whether the medical uses of cannabis and its derivatives outweigh the harmful effects is a question that needs to be explored. For the past 5000 years, cannabis has been used for medical purposes and misused for recreational purposes. In India, its use has been prevalent since around 1000 BC both for medical and religious purposes.

However, in India, as per the Narcotic Drugs and Psychotropic Substances Act, 1985, cannabis and its various forms – hashish, ganja, charas, bhang – are banned and their possession is deemed to be unlawful.^[2] Similarly,

the Food and Drug Administration of US (USFDA) also does not permit cannabis for medical use except in a few conditions where the synthetic cannabinoids have been approved for therapeutic purposes.^[3] Cannabis smoking has been an underreported, but a distinctly prevalent evil in our society with a prevalence of 3.9% in the age group of 15-64 years around the world. Worldwide about 180.6 million persons smoke Marijuana.^[4,5]

More than 60 plant-derived components of cannabis, also known as phytocannabinoids, have been isolated. Among these phytocannabinoids, the chief psychoactive constituent of cannabis has been found to be delta-9-tetrahydrocannabinol (THC) which can be found in concentrations of 0.2% in hemp fiber to about 30% in a hybridized variety of this herbaceous plant.^[6]

The components of cannabis, including cannabigerol (CBG), cannabinol (CBN), and cannabidiol (CBD), are not psychoactive as compared to THC. CBD, in particular, has been shown to have anxiolytic and antipsychotic effects as compared to THC that has been linked to psychosis.^[7] This has been attributed to their influence on different regions of the brain. CBD has also been shown to have anti-emetic and anti-inflammatory effects, It also has a lowering effect on the intra-ocular pressure.^[8]

The term medical marijuana is attributed to forms of marijuana which are either phytocannabinoids used medically or mixtures of THC and CBD produced in the laboratory.^[6,9] In addition, endogenous endocannabinoids

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and the endocannabinoid signaling pathways are an active area of research.

The commonly available cannabinoid products include dronabinol, nabilone, and nabiximols. Dronabinol and nabilone (both synthetic THC) have been approved by the USFDA for use. Nabiximol having THC: CBD in the ratio of 1:1 has also been approved in some countries.^[10]

The different preparations of cannabinoids used for medicinal purposes are in the form of oral formulations, inhalational (smoke) forms, and vaporized forms. Out of these, inhalation and oral ingestion are the common routes of administration for natural and synthetic cannabis derivatives.

In addition, sublingual, rectal, intrathecal, transdermal, intravenous, and ophthalmic routes have been explored.^[11]

Smoking of marijuana for recreational purposes leads to a sense of euphoria, altered perception, and relaxation, along with increased intensity of normal experiences such as eating food.^[5] Recreational use differs from the medical use of marijuana in not just the amount being used but also the goals of its use.^[12]

Recreational use of marijuana would involve untitrated concentrations usually in inhalational form taken for long periods of time for its psychotropic effects. On the other hand, medical use of marijuana is used for specific conditions in a titrated dosage through various routes of administration to achieve the expected clinical effects. In addition, the duration of usage is also monitored to prevent its abuse.^[13]

Cannabinoid intoxication severely impairs the processing speed, attention span, recall abilities, reaction time, and psychomotor abilities when used in higher doses.^[14] A withdrawal syndrome is also known with oral THC and smoked cannabis, which is characterized by the chief symptoms of insomnia, irritability, abdominal pain, and decreased appetite, with significant mood alterations only at higher dosages. Cannabis usage can also result in a state of drug dependency. The lifetime smoking of cannabis also has been shown to increase the risk of psychosis and schizotypal personality traits.^[7]

Marijuana smoking can lead to many respiratory symptoms including cough, increased sputum production, and wheeze in a variable proportion of cannabis smokers. It is also linked with pharyngitis, hoarseness, breathlessness, and exacerbation of bronchial asthma.^[15] The respiratory tract in cannabis smokers shows erythema and edema, along with increased secretions in the airways. Furthermore, cannabis has been shown to have acute bronchodilator effects; however, the effect is ill-sustained over 6-8 weeks and has slower onset and is less effective than salbutamol.^[16]

Cannabis smoking also causes increased resistance in central airways with symptoms like bronchitis with hyperinflation, but has minimal effects on Forced Expiratory Volume in 1st second (FEV₁) and airflow obstruction.^[15,17] Further, the association of cannabis smoking with airflow obstruction has not been found to be conclusive in recent studies.^[17,18] Larger airways are affected with increased risk of bronchitis and mucus production as compared to tobacco smokers, but there is practically little or no risk of chronic obstructive pulmonary disease (COPD). Heavy cannabis smoking has been shown to be occasionally associated with bullous emphysema, but the evidence is inconclusive.^[16]

Cannabis concentrates have been shown to cause more cytotoxicity, mutagenicity, and chromosomal damage as compared to tobacco concentrates.^[19] Surprisingly, even though these findings suggest otherwise, cannabis has not been shown to be associated with lung cancer when adjusted for tobacco smoking as the main confounding factor.^[20,21]

Medical marijuana has been used for specific medical conditions for variable duration. Its use may cause certain side effects which may be of concern. A systematic review of 31 studies has analyzed that 4779 adverse effects were reported while using a medicinal cannabinoid for 8-12 months. Most of these side effects were of non-serious nature (96.6% of the total number of adverse effects) with dizziness being the most common. These side effects were higher than in the control group [rate ratio (RR) 1.86, 95% confidence interval (CI) 1.57-2.21], whereas the serious adverse events (3.43%) such as relapse of multiple sclerosis (MS), vomiting, and urinary tract infection were found to be statistically non-significant between the two groups.

However, this review included studies of short duration only and medical cannabis administered by smoking was not included in this review since the adverse effects were not quantified in any such study.^[12]

It is clearly evident that most of the long-term effects of marijuana have been observed on use of marijuana for recreational purposes, as the use of medical marijuana has not been studied for a longer duration. Thus, it can be deduced that long-term effects of inhalational route of medicinal marijuana may be similar to those of recreational use of marijuana.

These effects clearly define a risk with marijuana usage, but there is another perception which needs to be looked at in terms of the various uses of cannabis congeners and different preparations that are being investigated as possible therapeutic alternatives. The use of smoked marijuana has been investigated for neuropathic pain with results showing that 9.4% THC produced mild but effective analgesia compared to placebo in a sample selected who had not responded to standard therapy.^[22]

Smoked marijuana with dosage and titration based on the number of inhalations is usually sufficient to produce clinical effects without the psychoactive adverse effects^[13] THC or CBD, when used alone or in combination, has been found to be more effective than placebo, especially in neuropathic pain.^[23] Further, a systematic review has revealed that the cannabinoids dronabinol, nabilone, and levonandradol are as effective as 50-120 mg of oral codeine.^[24] There is lack of data comparing inhaled cannabis or cannabis extracts to conventional pain medications for the relief of chronic non-neuropathic pain. Also, nabilone has been found to be less effective than dihydrocodeine in patients with neuropathic pain.^[25]

Randomized clinical trials using oral preparations for spasticity and neuropathic pain of MS patients have been shown to be effective with the range of efficacy of oral dronabinol similar to that of standard non-opioid drugs.

Many randomized controlled trials have supported that daily oral THC dosing can reduce pain and perceived spasticity in MS patients.^[26-29]

A study in cachectic AIDS patients has observed increase in appetite with dronabinol which lasted for 1 year as compared to placebo.^[30] Another recent study concluded that cancer patients with anorexia had improved appetite and taste with dronabinol compared to placebo.^[31] Unfortunately, the effect of dronabinol on cancer-related cachexia in long-term studies is not encouraging and there are no data on the effect of inhaled cannabis on cancer-associated cachexia.^[32,33]

The role of cannabinoids in chemotherapy-induced nausea and vomiting (CINV) has also been studied. Earlier studies showed encouraging results in controlling CINV. However, the current guidelines do not recommend cannabinoids as the first-line therapy.^[34,35] Nonetheless, FDA has approved the use of synthetic THC dronabinol and nabilone for the control of nausea and emesis caused due to cancer chemotherapy.^[21]

The role of cannabinoids has also been studied in fibromyalgia in a small number of patients with nabilone where it led to improvement in the quality of life of the patients with respect to pain and insomnia.^[36,37] Also, nabiximols have been shown to have small but significant analgesic effects with decreased disease activity in patients with rheumatoid arthritis.^[38]

Alternate delivery forms of medical cannabis, which include sublingual route with controlled-release spray devices, are licensed for cancer pain and MS associated neuropathic pain and spasticity in some countries of the world. Vaporized cannabis and capsulated forms with differing ratios of THC and cannabidiol are being studied as potential usable forms in the future.

The discovery of the endocannabinoid signaling pathways has been made, and their role in metabolism, inflammation, and cognition processes affecting the body tissues has also come to light. This clearly creates a possible future of cannabis-like drugs which can be used in multiple areas as conventional medicines.^[39]

The use of medical marijuana, whether in its oral form or the newer forms as formulated capsules or sublingual/vaporized sprays, does reduce the harmful effects of cannabis on the respiratory system, albeit with increasing cost and decreased efficacy.^[40,41]

The dependence and withdrawal caused by cannabis is far less severe than that caused by opioids and sedative hypnotics which also have high abuse potential. Thus, usage of legalized marijuana as a prescription drug to patients with conditions where it is an option should be viewed in terms of a risk-benefit analysis, keeping the broad background of risk-benefit ratios of other available agents in mind. Also, it would be ethically wrong to deny patients who are deemed to be suitable candidates for therapy due to the lack of legalization of medical marijuana.

In conclusion, further research with larger clinical trials is needed to assess the true benefits and risks of medical marijuana, which can be aided by the legalization and standardization of cultivation of cannabis. Recreational use of marijuana is harmful, causing pulmonary symptoms along with dependence, and therefore should be discouraged. On the other hand, medical marijuana has the potential to be used in many chronic debilitating diseases without significant adverse effects when used in a monitored setting.

However, the risk of abuse remains a burning issue in places where it has been legalized due to the misuse of medical marijuana for substance abuse.^[42] Strong and stringent measures are required to be kept in place before tinkering with the idea of legalization. In addition, it is imperative that the attitudes of the public and physicians at large are remoulded to use medical cannabis as a therapeutic alternative. Regardless of the implications of the use of medical marijuana, we conclude that it has the potential of providing relief and improved quality of life, therefore acting as a panacea and not a scourge.

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