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THERAPEUTIC POTENTIAL OF CANNABIS.

Jarnail Singh* and Janardhan Singh.

Professor, H. No. 10/8FM, Medical Campus Rohtak Haryana India.

*** Corresponding Author: Dr. Jarnail Singh**
Professor, H. No. 10/8FM, Medical Campus Rohtak Haryana India.

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ABSTRACT
Medical marijuana use is controversial in the American society. While the states move to legalize marijuana for medical or recreational use, research is needed to elucidate the adverse effects and potential therapeutic benefits of marijuana therapy. This review provides the current information on potential indications, pharmacology, toxicity, and contraindications for medical cannabis. Understanding of the potential uses of cannabinoids in various medical conditions will benefit the patients and healthcare providers. Legalization of marijuana use in 21 states of the US and the district of Columbia has called attention for health care providers.

KEYWORDS: Marijuana, cannabinoids, THC, dronabinol.

INTRODUCTION
Cannabis is defined as the flowering or fruiting tops of the cannabis plant the from which resin has not been extracted. Cannabis resin means separated resin whether crude or purified obtained from the cannabis plant. The use of cannabis for medicinal, ritual or recreational purposes results from the action of cannabinoids in the cannabis plant. Cannabinoids are derived plant source, phytocannabinoids, Cannabis sativa or Cannabis indica; endocannabinoids are neurotransmitters produced in brain and in peripheral tissues; and synthetic cannabinoids.[1] Cannabinoids also produce the unintended adverse consequences of cannabis. Cannabis contains at least 750 chemicals with 104 different cannabinoids and it is suggested that the chemicals may be useful for treating illnesses and symptoms.[2]

Some cannabinoids have approved therapeutic uses i.e. psychoactive cannabinoid THC (delta-9-tetrahydrocannabinol) for antiemetic and appetite stimulating properties and for multiple sclerosis in Canada, Denmark and the United States; and Sativex, a combination of THC and cannabidiol (CBD) has approval for spasticity in 25 countries. Potential therapeutic applications for non-psychoactive phytocannabinoids are for treating psychosis, affective and seizure disorders, inflammation, obesity and neurodegenerative disease.[3]

Cannabinoid compounds
Delta-9-tetrahydrocannabinol (delta-9-THC) is the primary active constituent in cannabis. Prominent psychotropic effects of THC limited its clinical use. Other cannabinoids include cannabidial (CBD), delta-8-THC,cannabigerol,delta-9-tetrahydrocannabivarin and cannabidivarin. A numer of synthetic compounds with cannabinomimetic activity have been synthesized.[4] These drugs are the potential therapeutic agents for a broad range of diseases. Dronabinol is an isomer of THC, approved by US FDA in 1985 for treatment of chemotherapy induced nausea and vomiting in patients not responding to the existing antiemetics; and for the anorexia and cachexia in patients with AIDS. Nabilone is a schedule-II THC analog, approved by US FDA in 1985 for treatment of nausea and vomiting and used off-label for analgesia. Nabiximols is a cannabis extract with 1:1 ratio of THC and CBD (2.7 mg THC+ 2.5 mg CBD). The drug has regulatory approval for pain medication in selective patients in 20 countries and is currently undergoing advanced Phase-III trial in the United States for treatment of cancer pain refractory to opioid therapy. Cannador is cannabis extract containing 2:1 ratio of THC and CBD. It is under study in Europe for treatment of anorexia and cachexia in patients with cancer.[5]

Cannabinoid pharmacokinetics
Cannabinoids undergo extensive metabolism by CYP450 2C9 and 3A4 forming at least 80 metabolites. Most of the metabolites are biologically inactive but some are active i.e. 11-hydroxy-THC. Glucoronide is the major urinary metabolite along with 18 nonconjugated metabolites. Plasma clearance of THC is quite high, but its rapid disappearance from blood is due to tissue redistribution or distribution into fat. THC and cannabinoids have a very long elimination half-life because of slow release. Terminal half-life of THC is estimated to 10-13 days. Inactive carboxy metabolites with terminal half-life 50 hours to 6 days, detected in

urine, serve as markers of prior marijuana use.[6] Onset of psychoactive or other pharmacological effects of marijuana is rapid after smoking and slower after oral doses. With smoking of marijuana THC is absorbed as an aerosol in seconds and delivered to brain rapidly and efficiently. Peak blood levels appear 10-30 minutes after smoking and formation of active metabolites may prolong peak onset and duration of psychological effects.[6]

When cannabis is ingested onset of action is delayed and variable lasting 5-12 hours. Peak effects may occur one hour or delayed upto 4-6 hours.[7] Oral bioavailability of THC, pure form or as THC in marijuana, is low **and** extremely variable 5% -20%. Oral THC undergoes first-pass metabolism resulting in reduced bioavailability. After oral dose formation of active THC metabolite, 11-hydoxy-THC may exceed delta-9-THC contributing to pharmacological effects of THC or marijuana.[8] Little 11-hydroxy-THC is formed after smoking. There is great variation in absorbed dose from smoked marijuana.[9] Experienced users are better able to regulate the amount of THC delivered to the lungs.

Cannabinoid biology, signaling in brain and peripheral tissues

Endocannabinoid system has four main components:

1. G-protein coupled cannabinoid receptors (CB1 and CB2)
2. Endogenous endocannabinoids that target receptors CB1 and CB2.
3. Enzymes that catalyze biosynthesis and metabolism of the endocannabinoids.
4. Mechanisms involving cellular accumulation of specific endocannabinoids.[1]

The receptor CB1 is expressed in brain and peripheral tissues with multiple functions. In brain G-protein coupled receptors mediate most of the psychoactive effects of THC in cannabis. CB1 receptors are enriched in cerebellum (cognition, coordination), hippocampus (learning and memory), cortex (cognitive function, executive function and control, integration of sensory input), basal ganglia (motor control and planning), ventral striatum (prediction and feeling of reward), amygdala (anxiety, fear, emotion), hypothalamus (appetitte, hormone levels, sexual behavior), brain stem and spinal cord (vomiting, pain).[10,11,12]

CB2 receptors are predominant on immune cells, hematopoietic system and other local cells and brain. In the brain CB2 receptors modulate the release of chemical signals engaged in function of immune system (e.g. cytokines). Activation of CB2 receptors by THC does not cause psychoactive effects.[13] CB2 receptors are a therapeutic target as they may circumvent adverse effects of cannabis or THC.

Function of endocannabinoid system in brain:

Endocannabinoids play a fundamental role in regulating pleasure, memory, thinking, body movements, awareness of time, appetite, pain, special senses and brain development.[14,15] Endocannabinoid signaling is crucial brain development. Endocannabinoid signaling may be susceptible to cannabis use during pregnancy and adolescence affecting brain structure and function. Endocannabinoids may contribute to developmental neuropsychiatric diseases with modified signaling e.g. autism, schizophrenia, bipolar disorder and depression.[15,16] THC and CBD inhibit neurogenesis in rodent brain is a process of potential relevance to wide range of cannabis induced adverse effects.[17]

Cannabinoids and CB1 and CB2 receptors show a neuroprotective role in brain by preventing damage due to mechanical, blood flow or other form of injury. Endocannabinoid system contributes to olfactory, auditory and pain sensations. A number of brain nuclei in medulla regulate appetite and nausea coordinating the sensory input from brainstem, vagal complex, vestibular apparatus and the peripheral organs.[18] Endogenous cannabinoids including cannabis and THC affect sleep patterns; and cannabis may be therapeutically useful in sleep disorders.[19] The endocannabinoid system has dose dependent antidepressant, anxiolytic and mood elevating effects.[20,21] Cannabis at high doses increases risk of depression and anxiety by down-regulating CB1 receptors.[22] Endogenous cannabinoids inhibit seizure susceptibility and exogenous cannabis has antiseizure activity. CBD has therapeutic potential as antiseizure drug without the psychoactive effects.[23] Cannabinoids can facilitate and degrade the learning processes depending upon the process involved. On the other hand, THC and cannabis decrease working memory by action in the hippocampus. The endocannabinoid system regulates motor pathways addressing the underlying pathology in neurological diseases associated with motor impairment.[24] CBI receptors are abundant in brain regions regulating motor function and coordination; and are down regulated in several neurological conditions.[25]

Functions of endocannabinoid sytem in peripheral tissues

Endocannabinoid signaling system is found in most of the peripheral tissues with potential medical applications of cannabinoids. CB1 and CB2 receptors are highly expressed on enteric nerves and enteroendocrine cells in the intestinal mucosa, on immune cells and enterocytes. CB1, CB2; and contribute to the development of common cardiovascular disorders. Expression of CB1 and CB2 is low in liver, working n opposite directions; CB2 receptors mediating several biological functions in liver cells and CB1 blockade contributing to beneficial metabolic effects. CB1 expression increases in pathological states promoting fibrogenesis, steatosis and cardiovascular complications of liver disease.

Endocannabinoids modulate functioning of immune cells through CB2 receptors providing a novel target for therapeutic manipulation.[26] In reproductive system endocannabinoid system regulates all critical stages of pregnancy through CB2 receptors; also sperm function and male fertility.[1] Endocannnabinoid signaling regulates skin functioning i.e. proliferation, differentiation, cell survival and immune responses.

Medical use of marijuana

Cannabis has been proposed to be beneficial in a broad range of CNS and other disorders. Potential therapeutic uses for cannabinoid are as follows.

Chronic pain: Cannabis and other cannabinoids are used as analgesic in patients in whom standard therapies are ineffective or intolerable or they are used as add-on therapy to current regimen.[27] These drugs act synergistically with opioids. Many cannabis analgesic studies showed more than 30% reduction in pain intensity.[28] Earlier trials suggested effective analgesia with cannabis in patients with neuropathic pain.[29] Inhaled THC has been shown to be effective in reducing pain of HIV associated distal sensory polyneuropathy.[30,31] Chronic pain was assessed in 28 studies in 2454 patients.[5,33,34] Thirteen studies evaluated nabimixol, 4 smoked THC, 5 for nabilone, 3 for THC mucosal spray, 2 dronabinol, 1 cannabis and 1 oral THC. The conditions causing chronic pain varied between studies (neuropathic pain 12, cancer pain 3, neurological conditions, HIV associated neuropathy, fibromyalgia, MS, rheumatoid arthritis).[27]

Musculoskeletal disorders: Studies generally suggested improvement in pain measures associated with cannabinoids. Reduction in pain was greater with cannabinoids than with placebo (average >30%). One trial assessed smoked THC and reported the greatest beneficial effect. Opioid sparing effect of cannabinoids have been reported in various chronic pain conditions.[34,35]

Nausea and vomiting due to chemotherapy: Synthetic THC analog nabilone and dronabinol received initial regulatory approval for chemotherapy induced nausea and vomiting based on improved outcomes over standard antiemetics used in 1980s.[36] Chemotherapy induced nausea and vomiting was assessed in 285 studies, 14 studies assessed nabilone (2 mg daily) and there were 3 for dronabinol (5-30 mg/day, 2 doses), 1 for nabiximols (8 spray/3hours), 4 for levonantradol and 6 for THC (5-60 mg/day).[37,38,39] Two studies also included a combination therapy of dronabinol with ondansetron or prochlorperazine. All the studies suggested a greater benefit of cannabinoids compared with both of the active comparator and placebo but without statistical significance. The average number of patients showing a complete nausea and vomiting response was greater with cannabinoids (dronabinol or nabiximols) than placebo. Results were similar for both dronabinol and nabiximols**.**

Appetite stimulation in HIV/AIDS infection: Appetite stimulation in HIV/AIDS patients was assessed in 4 studies using dronabinol.[40,41] There was some evidence that dronabinol is associated with an increase in weight as compared to placebo. However outcomes were assessed in single studies. Trials that evaluated marijuana and dronabinol found significantly greater weight gain with both forms of cannabinoid when compared with placebo.[40]

Spasticity due to multiple sclerosis (MS) or paraplegia: Many patients with multiple sclerosis have sought relief by cannabis use. The oromucosal spray cannabidiol appears efficacious in multiple sclerosis but it not yet approved for clinical use in the US.[42] Several clinical trials of cannabis in MS have demonstrated efficacy in reducing spasticity and pain.[43] Fourteen studies (2280 patients) have assessed spasticity due to MS or paraplegia.[44,45,46] Eleven studies (2138 participants) included patients with MS and 3 studies included patients with paraplegia (142 patients) caused by spinal cord injury.[30,47,48] Drugs evaluated included nabiximol, dronabinol, nabilone and THC/CBD. All the studies included a placebo control group. The studies generally suggested that cannabinoids were associated with improvement in spasticity. Cannabinoids (nabiximol, dronabinol and THC/CBD) were associated with a greater improvement on Ashworth scale of spasticity compared with placebo. cannabinoids nabilone and nabiximol) were also associated with greater improvement in spasticity using numeical rating scale.

Anxiety disorders: BergamkShield reported that cannabinoids were associated with a greater improvement in the anxiety factor of a visual analog mood scale in patients with generalized social anxiety disorder. Four studies in patients with chronic pain also suggested a greater benefit with cannabinoids (dronabinol, nabilone) in anxiety than placebo.[49,50]

Sleep disorders: Cannabinoids suppress sleep related apnea without respiratory depression and have shown beneficial effects on sleep quality.[51] Two studies evaluated cannabinoids (nabilone) specially for the treatment sleep problems.[32,33,53,54] One study reported a greater benefitof nabilone compared with placebo on the sleep apnea/hypopnea index. Another study compared nabilone with Amitriptyline in patients with fibromyalgia and suggested that nabilone was associated with improvement in insomnia. Nineteen placebo controlled trials for anther medications (chronic pain & MS) also evaluated sleep as an outcome. There was some evidence that cannabinoids may improve sleep in these patients. Cannabinoids, mainly nabiximols, were associated with a greater average improvement in quality and sleep disturbance.

Depression: No studies evaluating cannabinoids for fulfilled the inclusion criteria**.** treatment of depression fulfilled inclusion criteria.[33,49,54] Five studies for other

indications reported depression as an outcome measure. Four studies evaluated chronic pain and one study evaluated spasticity in MS patients. One trial assessed dronabinol, 3 assessed nabiximols and 1 assessed nabilone. These studies suggested no difference between cannabinoids (dronabinol & nabiximols) and placebo in depression outcomes. Endocannabinoid system has mood elevating and antidepressant effects.[21,55]

Psychosis: Cannabinoid compound was evaluated with amisulpiride or placebo in patients with psychosis. Trials found no difference in mental health the treatment groups.[56,57]

Glaucoma: Cannabis lowers blood pressure and may also reduce production of aqueous humour via cannabinoid receptor and thus temporarily lower the intraocular pressure..[58,59,60] One clinical study compared THC 5mg, CBD 20 mg, CBD 40 mg, oromucosal spray and placebo in patients with glaucoma.[61] The trial found no difference between placebo and cannabinoids on measures of IOP in patients with glaucoma.

Movement disorders due to Tourette Syndrome: Two placebo controlled trials (36 patients) suggested that THC capsule may be associated with a significant improvement in tic severity in patients with Tourette syndrome.[62,63]

Miscellaneous uses: Other potential but less characterized uses for CB1 and CB2 agonists include agitation in patients with Alzheimer's disease, amytropic lateral sclerosis (ALS), tardive dyskinesia induced by neuroleptic agents, gastrointestinal disorders including peptic ulcer, cholera, inflammatory bowel disease, cardiovascular disorders including hypertension, hemorrhagic cardiogenic shock, atherosclerosis, inhibition of angiogenesis and growth of tumors including gliomas, lymphomas; and lung, breast, thyroid, prostate and skin cancer.[64,65] Cannabinoids and CB1 and CB2 receptors display neuroprotective effects in brain by preventing or decreasing the severity of damage caused by blood flow or other injuries.[66]

Cannabis toxicity in man:

Cannabis and central nervous system (CNS)

Cognition and coordination: Acutely cannabis impairs cognitive function i.e. short term episodic and working memory, planning and decision making, response speed, accuracy and latency. Some studies also report increased risk -taking and impulsivity. Also cannabis impairs motor co-ordination, interferes with driving skills and increased risk of injuries. Complex human/machine performance can be impaired for 24 hours after smoking a moderate dose of cannabis.[67]

Psychosis and schizophrenia: Over last two decades cannabis use has been strongly associated with psychosis or schizophrenia. Cannabis can produce a full range of transient schizophrenia in healthy people. In those having a psychotic disorder cannabis may exacerbate symptoms, trigger relapse or have negative consequences during course of illness.[68] Heavy cannabis use can cause psychotic illness in susceptible individuals, also cannabis use is associated with lowering the age of onset of shizophrenia.[69] Symptoms of schizophrenia increase with cannabis use and strength.

Cannabis and peripheral tissues

Pulmonary disease and lung cancer: Chronic cannabis use is associated with an increased prevalence of symptoms of chronic bronchitis. Also, cannabis smoke does not appear to contribute to chronic obstructive pulmonary disease (COPD) nor its carcinogenic effects. Low level of cannabis exposure is not problematic but regular cannabis users are more likely to have chronic bronchitis and increased rate of respiratory infections and pneumonia.[70]

Cannabis use is associated with increased risk for myocardial infarction (MI), stroke and transient ischaemic attacks (TIA) during cannabis intoxication.[71]

Cannabis and carcinogenic potential: Cannabis smoke is carcinogenic in rodents and mutagenic in the Ames test. Cannabis smoke contains several of the carcinogens in tobacco smoke at upto 50 higher concentrations. Respiratory mucosa exposed to chronic cannabis smoke shows pre-neoplastic histological and molecular changes. Despite this there is no strong correlation between cannabis use and the development of cancers in man.[1]

Cannabis hyperemesis syndrome cases have been reported despite use of cannabis for antiemetic action. Patients exhibit a triad of symptoms: cyclic vomiting, chronic cannabis use and compulsive hot water bathing, attributable to heavy cannabis use.[72]

Evidence of cannabis use for medicinal use: Cannabis was used primarily for back pain, sleeping disorders, depression, injury generated pain and multiple sclerosis. Recent reviews and meta-analyses have weighed in the therapeutic indications for neurological diseases. One study from the UK reported that approximately 14-18% of MS patients used cannabis for symptom relief from pain, spasticity and insomnia.[73] MS patients who smoked cannabis displayed additional deterioration in cognition, including processing speed, memory and executive functioning.[74,75] Persons with HIV neuropathic pain report improvement in health from smoking cannabis.

A randomized, double-blind, placebo controlled crossover study in 16 painful diabetic peripheral neuropathy assessed short-term efficacy and tolerability of inhaled cannabis. There was a modest reduction in pain for low and moderate dose but a marginal effect a the highest dose.[76] In a cross-over design Ellis et al assessed smoked cannabis for HIV/AIDS neuropathy, and pain relief was greater with cannabis than placebo

with 46% having 30% pain relief with cannabis versus placebo (18%).[77] There is some interest in assessing therapeutic potential of cannabinoids in Alzheimer's disease (AD) but there are no RCTs with cannabis plant to treat symptoms of AD or progression of the disease.[78] Cannabis has been known for centuries to increase appetite and food consumption. CBI receptor has been shown to have role in central appetite control, peripheral metabolism and body weight regulation. Studies have shown that cannabis improves appetite, increases weight, and improves quality of life in patients with HIV/AIDS.[79] Cannabis and low dose dronabinol were well tolerated HIV-positive patients resulting in few physical symptoms. Cannabis and dronabinol significantly caloric intake in low bioelectrical impedance analysis (BIA) group but not in normal BIA group.[1]

There have been small clinical trials on use of cannabis in cancer patients. Antiemetic properties of cannabinoids led to approval of nabilone and dronabinol.[80] Some patients prefer smoking cannabis over oral cannabinoids because swallowing of pill is difficult while experiencing emesis, onset of relief is faster with smoking and the whole plant is more effective.[81]

SUMMARY AND CONCLUSIONS

Medical marijuana has become a hot topic in health care. The medical benefits of cannabis continue to be debated globally, for nearly 150 years. Initiatives to either legalize or prohibit marijuana use for medical purposes are being legislated by politicians. A comprehensive presentation of the scientific facts from evidence-based perspective is most needed. Cannabis were listed in the British, and alter in US Pharmacopeia with sedative and anticonvulsant effects, but they were removed a century later. The move revives cannabis as a medicine to alleviate pain, suizure disorders, enhance appetite in AIDS and HIV patients, for neurological and metabolic diseases, is driven by multiple factors. With the discovery of endocannabinoids and their receptors in brain and the peripheral tissues, the research for medicinal effects of cannabinoids has entered a modern context.

For psychoactive drugs such as cannabis, criteria for its approval as safe and effective medicine needs to be fulfilled along with cost-benefit analysis to weigh its therapeutic potential and detrimental effects to the society.

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