Journal of
Addiction Research & Therapy
ISSN: 2155-6105

Oberbarnscheidt and Miller, J Addict Res Ther
2017, S11:S11
DOI: 10.4172/2155-6105.1000S11-011

Research Article OMICS International

Marijuana-Is It a Medicine?

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Received date: November 21, 2016; **Accepted date:** December 02, 2016; **Published date:** December 09, 2016

Abstract

This review is based on literature search to determine the risks and benefits of marijuana as a medical agent and the role for marijuana in mainstream medicine. “Marijuana" is the natural form of cannabis derived from the Cannabis sativa plant and refers specifically to the dried leaves and flowering tops or "herbal cannabis”. Other terms for marijuana are cannabis or hemp.

Current clinical studies do not focus on the natural form of marijuana, but evaluate synthetical forms of THC instead. Marijuana is a schedule I substance by federal law with high potential of addiction and no medical benefit which limits research studies and forbids clinical use. However, the synthetically form THC cannot be compared with the natural form of marijuana and vice versa.

Unlike most medications on the market, marijuana does not have only one or two active agents. Natural forms of marijuana are derived from the plant, Cannabis sativa, and consist of over 400 compounds including flavonoids and terpenoids and more than 60 cannabinoids other than delta-tetrahydrocannabinol (THC). Many of these compounds are not understood and their effects and adverse effects unknown.

Keywords: Marijuana; Toxic effects; Patient; Cannabis

Introduction

In the last decade marijuana became legal in some states in contradiction to federal law and utilized in the treatment of medical conditions. This is very concerning because marijuana is the most commonly used illicit drug in the United States: about 12% of the US population used cannabis in the last year [1,2]. Importantly “Medical Marijuana” did not originate in medical practice and was not based on scientific medical research [2,3] (Table 1).

HIV/AIDS	Multiple Sclerosis (MS)	Post-traumatic Stress Disorder (PTSD)	Glaucoma
Hepatitis C	Amyotropic Lateral Sclerosis (ALS)	Nail Patella	Agitation in Alzheimers disease

Table 1: Marijuana is available legally as “Medical Marijuana” in an increasing number of states in the US for so called “debilitating medical conditions” [3,7].

Even though marijuana is used for those medical indications, clinical studies do not support marijuana’s benefit or adequately evaluate toxicity from marijuana. Studies were not controlled, contained very small patient populations and too short follow up periods for treatment of chronic conditions. Studies showing some analgesic effect included patient populations with low-grade functioning and high percentage of additional drug use including alcohol, opioid or stimulant use [1,4-6].

Marijuana causes a wide range of mental and physical and toxic effects. The risks and toxic effects outweigh the benefit by far in the majority of medical indications. Marijuana is not a safe medication due to it’s unpredictability as a drug, which can cause long-term harm in the patient.

This review focuses on the chronic use of marijuana and the treatment of pain and medical conditions. Therefore many of the studies regarding marijuana were not considered because they were not relevant to standard medical practice.

General characteristics of marijuana

Marijuana has been used for thousands of years for various “medical conditions”. This review focuses on the use of the natural form of marijuana, which stems from dried parts of the cannabis sativa plan and is predominantly utilized in smoked form [2,7].

Other possible routes and forms of “natural” marijuana for consumption are oral with food or teas, transdermal in patches or as a vaginal or rectal suppository.

There is only very limited number of studies published utilizing the natural form of marijuana. The majority of studies on “marijuana” or “cannabis” use synthetic THC in their study population. Only the synthesized forms of marijuana are FDA approved. The two FDA

indications are appetite enhancer in AIDS and spasticity in Multiple Sclerosis. The natural form of smoked marijuana has not been approved by any regulatory agency worldwide. It is a schedule I substance with high potential for addiction and no medical benefit [3,7].

Studies analyzing the effect of marijuana on the treatment of chronic pain are including too small numbers of patients and do not address the long-term outcome resulting in the use of marijuana especially considering its use in chronic medical conditions. The majority of studies have a follow up period of only days [8,9].

Unlike most medications on the market, marijuana does not have only one or two active agents. Marijuana consists of over 400 compounds including flavonoids and terpenoids and more than 60 cannabinoids other than the active form of delta-tetrahydrocannabinol (THC). Evidence shows that many of these compounds are not understood and their effects and toxic effects unknown. Marijuana is not a medicine as it is an unpredictable drug, which causes longterm harm in the patient as do opioid medications [2,3].

Due to marijuana's pharmacokinetic properties, it is highly dangerous in terms of the duration of the effects and the duration that it remains in the users system. Marijuana is very lipo-soluble and tends to accumulate in adipose tissue together with its derivate. Therefore marijuana is released into the body long after last ingestion, resulting in more potent and persistent effects and adverse effects in the users. (3)

Marijuana causes a wide range of highly toxic physical and mental effects and can cause long-term impairment and induce the onset of psychiatric conditions [2,3] (Table 2).

Marijuana is an addicting drug and tolerance and dependence occur. The attempt to discontinue does create a set of symptoms called "marijuana abstinence syndrome".

The aberrant, drug seeking, behaviors in the patient and the desire for the "high" are the main motives and demand for the use of marijuana in medicine [2].

1. Proof of beneficial effects and safety in at least two clinical trials
2. Well defined and measurable in its ingredients
3. Consistency of ingredients and effects from one unit to the next
Goal: Ensure that drugs marketed in the US are safe and effective

Table 2: FDA requirements for drug approval.

Due to the chemical structure and components in the smoked marijuana's raw plant form, these criteria are not met [3].

This process does not follow common practice of distribution of a medication. No medical supervision oversees, evaluates and administers the drug. Also, there is no dosing recommendation available and no follow-up or monitoring of drug levels are occurring by a physician like it usually occurs in medication management. Therefore marijuana can't be called a "medication" according to medical practice and customs as well as the FDA requirements [7] (Table 3).

1. Download application form for medical marijuana card, fill out form
2. Find physician for signature on form
3. Pay fee
4. Start home growing or buy off street. NO PHARMACY
5. Start using at own dose desire, financial abilities.
6. No further monitoring occurs, no follow-up.

Table 3: Process to obtain medical marijuana certification (most states).

Marijuana in pain management

Pain is a major health concern in the US that affects 116 million Americans and has a high socio-economic impact on the US economy through its direct costs for medication and doctor's visits as well as indirect costs through absence from work or school and other losses [4].

Cannabis is a central acting substance, which predominantly acts in the brain as well as in the spinal cord. Through antagonist effect on the marijuana receptors it interacts with pain pathways, which lead to the hypothesis that it would be beneficial in pain management [3].

Studies with the natural form of marijuana are rare and mostly conducted outside the US. Marijuana research is limited by federal regulations of the drug being classified as a schedule I drug with high potential of addiction and no medical benefit [7].

The comparison of the efficacy of marijuana in current literature is complicated by the nomenclature. Articles are claiming to analyze the efficacy of "marijuana" in pain management or "cannabis" but the majority actually administered the synthetical form of marijuana, THC or cannabinoids. The synthetical forms of THC cannot be compared with the natural form of marijuana and vice versa [10].

Clinical studies of "natural" marijuana in pain management

Very few studies are available in the US utilizing the natural form of marijuana as smoked or eaten by consumers. The following studies represent the current research for the natural forms of smoked marijuana. Many studies highlight the use of other addicting drugs and low-functioning in patients. Also, the pain/medical conditions were poorly defined and highly subjective.

A randomized controlled clinical trial by Ware et al. in 2010 analyzed the effect of smoked cannabis in patients with neuropathic pain or post-surgical pain. 23 patients were receiving single 25 mg doses of herbal marijuana containing either 0% THC (placebo) or 9.4% THC through a pipe three times daily and would be followed up for 5 days. The pain was assessed using an 11-point numeric scale. Patients reported a slight improvement in pain perception. Pain intensity averaged 5.4 on the pain scale in the marijuana group versus 6.1 in the placebo group. Various side effects were reported: headache, dry eyes, burning sensations in the areas of neuropathic pains, dizziness, numbness and cough. The feeling of being "high" and euphoria was reported at least once per patient during the 5 day period. The criticism of this study is that the patient population is very small and the follow-up period of 5 days was very limited to evaluate chronic pain conditions [8].

The experience of feeling "high" points out the addictive potential of marijuana and the aberrant behaviors that result from this experience in the user to acquire the "high" again. The feeling of high or being "stoned" combined with a short moment of euphoria leads to impaired cognition and judgment. A study by Walsh et al., interviewed 628 marijuana users in Canada for their motives of acquiring the drug: 82% of the participants stated that they had used marijuana before for non- therapeutic purposes [11].

Another study by Ashrafioun et al. in Ohio interviewed medical marijuana users for their reasons of use and functionality. The main reason claimed was pain. Eighty percent of the study population was unemployed, 40% with previous history of incarceration. The interviewed medical marijuana users had a very high rate of additional drug addictions including alcohol, tobacco, heroin, prescription opioids and sedatives [12].

Marijuana is also discussed to have a role in augmentation on opioid therapy and to limit the use of opioids. The POINT study of 1514 people in Australia claimed that marijuana has an opioid sparing effect in patients with non-cancer pain consisting of arthritis, back pain, fibromyalgia, visceral pain or headaches. Taking a closer look at the compared patient populations, alarming differences become obvious [12].

The patient population that received cannabis had a significantly higher percentage showing low-grade socio-economic functionality. Seventy-three percent of the patients utilizing marijuana were unemployed versus 45% in the non-marijuana group. Also, the marijuana group had a significantly higher percentage of additional drug addictions. The rate of alcohol use disorders and tobacco use was twice as high, amphetamine use six-times as high and illicit opioid use three times as high compared to the non-marijuana group. The patients in the marijuana group were also on significant higher doses of pre-existing opioid medications and had a higher rate of co-medications with benzodiazepines and a higher rate of previously reported non-compliance [13].

Studies on synthetical forms of marijuana in pain management

Animal studies

Only animal models have shown some anti-nociceptive and anti-hyperalgesic effects after systemic administration of synthetic THC and cannabinoids for neuropathic and inflammatory pain. Those studies evaluate mostly the response of the animal to painful stimuli by motor activity. However, systemic administered cannabinoids can produce immobility and catalepsy in animals, which severely impacts the animal's motor response [14].

Human studies

Studies utilizing synthetical forms of marijuana reveal very inconsistent data. In the majority of studies there was no significant benefit observed, others described cases of hyperalgesia. Multiple studies have proven that there is no beneficial effect of marijuana in pain management [2,15,16].

Clinical trials evaluating the semi-synthetical form (Sativex) did not find an analgesic effect of Sativex superior to placebo in patients with pain from diabetic neuropathy [3].

Another study looked at the analgesic effect of THC in cancer patients. The study compared to placebo, doses of 15-20 mg THC provided analgesic effects over a 6 h period, which was equivalent to the analgesic effect of 120 mg codeine. Patients reported severe sedation though, even more severe than in codeine and in addition depersonalization [17].

There are also experimental studies performed on healthy individuals. One study in Switzerland exposed 12 healthy individuals to painful stimuli including transcutaneous electrical stimulation, heat and cold pressure. Volunteers were receiving either placebo or 20 or 30 mg THC prior to painful stimuli. There was no significant pain reduction reported in the group receiving THC [5]. Long-term studies about the outcome are not yet available. Studies lack washout periods from previous drugs/medication use occurring and there are overlaps in the patients with additional parallel use of other illicit drugs [13,17].

Marijuana as appetite enhancer in cancer patients

The review of literature did not reveal clinical studies utilizing the smoked "natural" marijuana. Synthetical cannabinoids are found to be beneficial in the treatment of nausea and vomiting in patients undergoing chemotherapy [6].

Tramer at al reviewed 30 randomized trials were oral nabilone and oral dronabinol were tested, including a total of 1,366 patients, comparing cannabinoids versus placebo and versus other antiemetics metoclopramide, chlorpromazine, triethylperazine and domperidone. The group found an antiemetic benefit superior to the conventional antiemetics except for patients receiving very low or very high emetogenic chemotherapy, which were not specified. A broad variety of side effects were reported: feeling "high" marked sedation, drowsiness, depression, hallucinations, paranoia and hypotension [6].

The therapeutic benefit of THC in cancer patients considering the side effect profile, as described below, from the oral cannabinoids is very questionable. There might be a potential role for THC or natural marijuana in palliative cancer care in hospice setting since sedation might be beneficial in end of life situations [6].

In addition, marijuana and its cannabinoids are carcinogenic by themselves and linked to an increased incidence of certain cancers for example leukemias, gliomas or rhabdomyosarcomas [2,3].

Marijuana in AIDS patients

Marijuana is used in AIDS patient as an appetite enhancer and to help with HIV induced cachexia. Only the synthetical forms of THC are FDA approved for this indication.

The Institute of Medicine concluded in its March 1999 report titled "Marijuana and Medicine: Assessing the Science Base" that the relationship between marijuana smoking and the natural course of AIDS is of particular concern because HIV patients are the largest group who report using marijuana for medical purposes. Marijuana use has been linked both to increased risk of progression to AIDS in HIV-seropositive patients and to increased mortality in AIDS patients [18].

Among the most compelling concerns regarding marijuana smoking in HIV/AIDS patients are the possible effects of marijuana on immunity. Reports of opportunistic fungal and bacterial pneumonia in AIDS patients who used marijuana suggest that marijuana smoking

either suppresses the immune system or exposes patients to an added burden of pathogens [18].

Marijuana in multiple sclerosis (MS) patients

The synthetic forms of THC have shown little concrete evidence that cannabis treats MS symptoms such as ataxia, tremors, spasticity [2,15].

Vaney et al. followed 50 patients with MS regarding their MS associated symptoms spasms and mobility after oral THC administration and found subjectively reported decrease in spasm frequency and improved mobility. While other studies did not reveal any improvement in the subjective reported muscle spasms at all [15].

A structural MRI study by Romero et al. evaluated 20 MS patients who were smoking marijuana with the Brief Repeatable Neuropsychological Battery and structural MRI scans and compared the data with 19 matched non-cannabis-smoking MS patients. The MRI in the cannabis smoking MS patients revealed gray matter volume loss in thalamus, basal ganglia, medial temporal and medial prefrontal regions, and white matter volume loss in the fornix. These imaging findings correlated with extensive cognitive impairments in the cannabis versus the non-cannabis MS group [19].

Marijuana in other medical indications

Marijuana is legalized in several states for the following deliberating conditions [7]

Depression

Contrary to the user's belief that marijuana alleviates depression, it actually worsens depression and is frequently reported as side effect in studies utilizing synthetical forms of marijuana for pain management. No clinical studies have shown any benefit in depression [20]. Rowe et al. showed that marijuana use worsens depression in females and increasing consumption of marijuana leads to higher level of depression and greater suicidal ideations [21].

Marijuana alters the patient's mood and perception. The feeling of being "stoned" and short episodes of euphoria are followed by worsened depression and impaired judgment [1,2,21].

Anxiety

Marijuana has no benefit in the treatment of anxiety; as a matter of fact it increases the level of anxiety and induces paranoia. Panic attacks are the most frequent anxiety state syndrome and about 30% of user's experiences acute anxiety reactions [21]. The frequent use of marijuana is associated with long-lasting anxiety symptomatology. A clinical study revealed that 21% of the interviewed marijuana users experienced high levels of anxiety states and several cases of agoraphobia and panic disorders are described [1,21].

Glaucoma

Regarding glaucoma the studies are very limited regarding their sample sizes. One study analyzed 18 patient's intraocular pressure after a single dose of smoked THC and found a reduction in the pressure. The decrease in ocular pressure was short in duration. If marijuana would be used for therapy it would require frequent re-administrations of smoked marijuana during the day, which bears an unacceptable risk regarding marijuana's side effect profile [9].

There is also evidence that marijuana lowers the user's blood pressure, which is thought to mediate the lowered intra-ocular pressure in glaucoma patients. This mechanism of action can potentially be harmful since it might cause poor perfusion of the optic nerve and generalized hypotension [9].

Alzheimers disease

Studies have already confirmed that marijuana impairs cognition [2,3] Thus, the indication to use marijuana raises major concerns since Alzheimer patients have an impaired cognitive function and often times are not capable to make their own decisions. To administer marijuana to this patient population and make them "stoned" and sedated seems unethical similar to the use of antipsychotics to control their behaviors. Nursing staff often times describes the patient "cooperative" when they are sedated and sleeping excessively. Therefore there is serious doubt for the use of marijuana as treatment in Alzheimers patients (Table 4).

Lung	Smoking marijuana causes severe lung damage. Compared to smoking tobacco one third more tar gets retained in the lungs. In short term marijuana use broncho-dilation has been reported, while with long-term use obstructive disease has been reported.
Heart	The use of cannabis increases the risk of heart attack. It causes ischemia by an almost fivefold increase in blood carboxyhemoglobin, which interferes with the hemoglobin's ability to transport oxygen within the body. Marijuana may also cause orthostatic hypotension with the danger of episodes of faints and falls.
Cancer	Cannabis is carcinogenic. Cancers associated with the use of cannabis are gliomas, prostate and cervical cancers. In pregnant women increased incidents of leukemia, rhabdomyosarcomas and astrocytomas are lined to the cannabis use.
Anxiety	Frequent marijuana use is related to panic and social anxiety disorders.
Psychosis	The use of cannabis increases the likelihood of schizophrenia and in schizophrenic patient's increases the rate of re-hospitalizations and greater impairment in psychosocial function. It can cause mania-like psychosis and precipitate a manic episode in bipolar patients.
Adolescents	Attention and memory problems are reported through intoxication with cannabis but also after periods of abstinence. The use of cannabis increases the rate of drop outs in school, high risk sexual behaviors with multiple sexual partners and increases the susceptibility towards other illicit substances. There is an association of ADHD and conduct disorders. A large, long-term study in New Zealand had shown that teenagers smoking marijuana heavily had an average of 8 point decrease in their IQ at age 13 and 38.
Judgement	Marijuana significantly affects judgment, motor coordination and reaction time. Studies have shown a correlation between blood THC concentrations and driving ability.

Pregnancy	Cannabis use during pregnancy leads to delays in neurological development. Babies born of woman who used cannabis respond differently to stimuli, have a high-pitched cry and tremble more. Some research also suggests that THC is excreted into the breast milk in moderate amounts.

Table 4: Physical and mental effects of marijuana.

Marijuana is an addicting drug

Beside the adverse effects, cannabis does create dependence and tolerance and addiction. Among daily users up to 50% are showing signs and symptoms of addiction. More than 50% of regular users experience withdrawal symptoms, so called "marijuana abstinence syndrome" [2].

The treatment for withdrawal is mostly behavioral interventions, including cognitive-behavioral therapy and motivational incentives. In the acute withdrawal anxiolytic medications for example benzodiazepines and antipsychotics can be used short term for the symptomatic treatment. The goal is to prevent severe agitations and improve the compliance in the patients (Table 5).

Marijuana use induces tolerance with accompanying down-regulation and desensitization of type 1 cannabinoid receptors with repeated exposure. The earlier literature suggested tolerance occurs after repeated administration of THC in man, but these studies were poorly controlled [3].

Anxiety	Decreased Appetite
Headaches	Insomnia
Irritability	Muscle Tension
Nausea	Nightmares
Unpleasant or Vivid Dreams	

Table 5: Symptoms of marijuana abstinence syndrome.

Questions

Examining the long list of serious toxic effects, marijuana in the smoked plant form is not a drug that should be considered in the treatment of pain or any other medical condition.

Clinical studies have not shown any convincing benefit in the treatment of various medical conditions. Clinical studies show a high rate of pre-existing marijuana addiction as well as addictions to other drugs.

The reasoning behind the prescribing of marijuana is not based on medical indications; it is based on the subjective demand for marijuana by the patient [2].

Should we give the patients the autonomy to decide their own treatment plan? Looking at other medical specialities where do patient influence their medication choice as they do for marijuana. Marijuana is highly addicting and users seek for the "high". Marijuana alters the user's perception and alertness but not pain level. Some articles call this feeling of being "high" improved quality of life. This is a very questionable definition when considering the overall low level of functioning in the users [2].

Should we allow the use of 'Medical Marijuana" without FDA approval? Marijuana clearly does not fulfill the FDA requirement to be called a medication. Marijuana's ingredients are poorly known and not consistent from one unit to the other. The route of acquiring cannabis and its distribution through the sales on streets or home-grown is not compatible with a "regular medication". Also, there are no dosing guidelines available and no actual medical monitoring is occurring by the physician of the actual medical condition [2,3,7].

Conclusion, examining the current evidence available for the treatment of chronic pain with cannabis means more risks than benefit. Also there is little data available about the long-term outcome of chronic marijuana use. Medical marijuana has adverse effects increasing the risk for psychosis, heart disease, at least three different cancers and impaired judgment.

Another concern is marijuana's pharmacology with the more than 421 chemical compounds and more than 60 cannabinoids with the majority of them not known in their effects and toxicity. The lipophilic quality of marijuana bears enormous risks through redistribution of the drug and potentiation of marijuana in the user with additional use or prolonged effects [1-3].

An additional risk with the use of marijuana is the interaction with other drugs especially since many marijuana users have multiple medical conditions. Marijuana is metabolized through CP450 in the liver [1]. Potentiated CNS depressant effects occur in combination with benzodiazepines, opioids, muscle relaxants or barbiturates. Marijuana decreases the efficacy of other medications for example protease inhibitors, theophylline and antipsychotics. Other drug levels become increased for example SSRIs and lithium [16].

Pain has a large socioeconomic impact on the US economy but legalizing marijuana is not the solution to improve the balance since smoked produces additional costs. Marijuana users have more sick days than others due to physical and mental toxicity. Also, additional costs accumulate due to loss of productivity and missed worked days as well as costs related to the direct health care and disability caused by marijuana.

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This article was originally published in a special issue, entitled: **"Marijuana: Clinical, Research, Policy"**, Edited by Norman S Miller