MEDICAL MARIJUANA: BASIC SCIENTIFIC VIEW

OWUSU NYARKO RICHARD[1] , OWUSU BOATENG PAUL[2]
[1]MDStudent, Doctor of Medicine & Surgery, Donetsk National Medical University, Kirovograd, Ukrain.
[2] MBBS Student, Liaoning medical university, China
Email - richardnyarko91@yahoo.com

Abstract: *Medical cannabis, or medical marijuana, can refer to the use of cannabis and its cannabinoids to treat disease or improve symptoms. The use of cannabis as a medicine has not been rigorously scientifically tested, often due to production restrictions and other governmental regulations. There is limited documented evidence suggesting cannabis can be used to reduce nausea and vomiting during chemotherapy, to improve appetite in people with HIV/AIDS, and to treat chronic pain and muscle spasms. But still medical cannabis has some benefits for the human system development, current scientific investigations with documented approved evidence show a tremendous benefit in the use of supervised and measured amount of marijuana usage prompting most states in the America to legalise it.*

Key Words: *Tetrahydro cannabinoids (THC), Cannabis, smoking, respiratory disease, Neurological disease, cannabidiol (CBD), cannabinol (CBN), cannabicyclol (CBL), Multiple sclerosis (MS), food and drugs authority (FDA)*

1.0 INTRODUCTION:

Scientific study of the chemicals in marijuana, called cannabinoids, has led to two FDA-approved medications that contain cannabinoid chemicals in pill form. Continued research may lead to more medications. Because the marijuana plant contains chemicals that may help treat a range of illnesses or symptoms, many people argue that it should be legal for medical purposes. In fact, a growing number of states have legalized marijuana for medical use. The U.S. Food and Drug Administration (FDA) has not approved smoked cannabis for any condition or disease as it deems evidence is lacking concerning safety and efficacy of cannabis for medical use. The FDA issued a 2006 advisory against smoked medical cannabis stating: marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision.
A 2016 review assess the current status and prospects for development of CBD and CBD-dominant preparations for medical use in the United States, examining its neuro - protective, antiepileptic, anxiolytic, antipsychotic, and anti-inflammatory properties.

2.0 METHOD:

Sample research where taken from scientific data from other works done and published in peer reviewed journals. They were analysed, criticized constructively, appraised and some which the writers deem fit was taken as a reference on this work. Stratified and probity of empirical data and cross sectional surveys done on the subject matter was also revised by the authors in bringing out the final write up.

3.0 DISCUSSION:

Medical cannabis can be administered using a variety of methods, including liquid tinctures, vaporizing or smoking dried buds, eating cannabis edibles, taking capsules, using lozenges, dermal patches or oral/dermal sprays. Synthetic cannabinoids are available as prescription drugs in some countries; examples include: dronabinol and nabilone. Recreational use of cannabis is illegal in most parts of the world, but the medical use of cannabis is legal in certain countries, including Austria, Canada, Czech Republic, Finland, Germany, Israel, Italy, the Netherlands (where it is also legal recreationally), Portugal and Spain. Australia is currently in the process of passing a law which would allow the use of marijuana for medical and scientific purposes. In the United States, federal law outlaws all cannabis use, while 25 states and the District of Columbia no longer prosecute individuals for the possession or sale of medical marijuana, as long as the individuals are in compliance with the state's medical marijuana sale regulations. However, an appeals court ruled in January 2014 that a 2007 Ninth Circuit ruling remains binding in relation to the ongoing illegality, in federal legislative terms, of Californian cannabis dispensaries, reaffirming the impact of the federal Controlled Substances Act.

Types:

Many different cannabis strains are collectively called medical cannabis. A Cannabis plant includes more than 400 different chemicals, of which about 70 are cannabinoids. In comparison, typical government-approved medications contain only 1 or 2 chemicals. The number of active chemicals in cannabis is one reason why treatment with cannabis

is difficult to classify and study.Using a THC-dominant strain/breed can show anecdotally that it may help people with insomnia (and other sleep disorders) get more rest, and that it could reduce the severity of tics in people with Tourette syndrome, yet the same strain could induce psychosis in a person with a psychiatric disorder. A 2014 review stated that the variations in ratio of CBD to THC in botanical and pharmaceutical preparations determine the therapeutic vrs psychoactive effects.

Pharmacology:

The genus Cannabis contains two species which produce useful amounts of psychoactive cannabinoids: Cannabis indica and Cannabis sativa, which are listed as Schedule I medicinal plants in the US. A third species, Cannabis ruderalis, has few psychogenic properties. Cannabis contains more than 460 compounds; at least 80 of these are cannabinoids – chemical compounds that interact with cannabinoid receptors in the brain. The most psychoactive cannabinoid found in the cannabis plant is tetrahydrocannabinol (or delta-9-tetrahydrocannabinol, commonly known as THC). Other cannabinoids include delta-8-tetrahydrocannabinol, cannabidiol (CBD), cannabinol (CBN), cannabicyclol (CBL), cannabichromene (CBC) and cannabigerol (CBG); they have less psychotropic effects than THC, but may play a role in the overall effect of cannabis. The most studied are THC, CBD and CBN.

Forms of Medical Marijuana:

Users smoke medical marijuana in paper-rolled cigarettes or pipes. You can also brew it into a beverage, eat it in cooked foods, or take it in pill form. The effects of a marijuana pill can be strong and long-lasting. This makes it hard to predict how it will affect a person. It can also be inhaled it through vaporizers. Cannabinoid receptors have also been found in skin. Some use topical marijuana for pain and inflammation. More research is needed.

Where Medical Marijuana is Legal?

California voters were the first to legalize medical marijuana, in 1996. It's now legal in almost half of U.S. states. If you live in a state where it's legal and your doctor has given the approval, you can buy it from an authorized seller known as a dispensary. Some people may legally grow their own medical marijuana. Australia has legalized it in the research laboratories for clinical trials and medical use but under supervison of a medical doctor.UK, Canada and some European countries are working scientifically to help them to strong legal decisions on it. No country in Africa has raisedmajor issues on researching medical cannabis and its potential benefits to the health industry and the general economy. Although basic discussions started in Ghana since November 2015 through the mental health authority and some stakeholders in the health care industry, lack of funding, basic but specialized research laboratories and skilled labour on the subject matter has become a set- back.

Medical Marijuana for Children:

Some studies suggest medical marijuana may help relieve seizures in children with hard-to-treat epilepsy. A type of medical marijuana known as Charlotte's Web may help kids without getting them high, because the strain has very little THC. Despite a federal ban, many states allow use of medical marijuana to treat pain, nausea and other symptoms. Marijuana is made from the dried leaves and buds of the Cannabis sativa plant. It can be smoked, inhaled or ingested in food or tea. Medical marijuana is also available as a pill or oil.

In the U.S. medical marijuana or medical cannabis is legal in a growing number of states to ease pain, nausea and other side effects of medical treatments, as well as to treat some diseases. Depending on why a person is using medical marijuana, treatment may be short term or continue for years under supervision of a physician.

4.0 ANALYSIS:

Physical and Chemical Properties of Marijuana (cannabis)

Smoking is the means of administration of cannabis for many consumers and the most common method of medical cannabis consumption in the world. It is difficult to predict the pharmacological response to cannabis because concentration of cannabinoids varies widely as there are different ways of preparing cannabis for consumption (smoked, applied as oils, eaten, infused into other foods, or drunk) and a lack of production controls. The potential for adverse effects from smoke inhalation makes smoking a less viable option than oral preparations. Cannabis vaporizers have gained popularity because of the perception among users that less harmful chemicals are ingested when components are inhaled via aerosol rather than smoke. Cannabinoid medicines are available in pill form (dronabinol and nabilone) and liquid extracts formulated into an oro - mucosal spray (nabiximols). Oral preparations are problematic due to the uptake of cannabinoids into fatty tissue, from which they are released slowly, and the significant first-pass liver metabolism, which breaks down Δ9THC and contributes further to the variability of plasma concentrations. The National Institute on Drug Abuse (NIDA) states that so far, researchers have not conducted enough large-scale clinical trials that show that the benefits of the marijuana plant (as opposed to its cannabinoid ingredients) outweigh its risks in patients it is meant to treat. In 2015 American Society of Addiction Medicine wrote

that legalization of cannabis in some states but not others provides a unique opportunity for a thorough investigation into the societal and public health impact of broader cannabis use. American Medical Association in 2015 stated that there are not enough large-scale studies on cannabis, while Office of National Drug Control Policy opposes legalization of marijuana and other drugs because legalization would increase the availability and use of illicit drugs, and pose significant health and safety risks to all Americans, particularly young people. The FDA finds that cannabis does not meet the criteria for accepted medical use due to lack of evidence regarding safety and the high risk of abuse.

4.2 MEDICAL USES:

Medical cannabis has several potential beneficial effects. Evidence is moderate that it helps in chronic pain and muscle spasms. Lesser evidence supports its use for reducing nausea during chemotherapy, improving appetite in HIV/AIDS, improving sleep, and improving tics in Tourettes syndrome. When usual treatments are ineffective, cannabinoids have also been recommended for anorexia, arthritis, migraine, and glaucoma.

Nausea and vomiting:

Medical cannabis is somewhat effective in chemotherapy-induced nausea and vomiting (CINV) and may be a reasonable option in those who do not improve following preferential treatment. Comparative studies have found cannabinoids to be more effective than some conventional anti - emetics such as prochlorperazine, promethazine, and metoclopramide in controlling CINV but these are used less frequently because of side effects including dizziness, dysphoria, and hallucinations. Long-term cannabis use may cause nausea and vomiting, a condition known as **cannabinoid hyperemesis syndrome.**

Dementia:

Cannabinoids have been proposed to have the potential for lessening the effects of Alzheimer's disease. A 2012 review of the effect of cannabinoids on brain ageing found that clinical evidence regarding their efficacy as therapeutic tools is either inconclusive or still missing. A 2009 Cochrane review said that the one small randomized controlled trial that assessed the efficacy of cannabinoids in the treatment of dementia had poorly presented results and did not provide sufficient data to draw any useful conclusions.

Diabetes:

There is emerging evidence that cannabidiol may help slow cell damage in diabetes mellitus type 1. There is a lack of meaningful evidence of the effects of medical cannabis use on people with diabetes; a 2010 review concluded that the potential risks and benefits for diabetic patients remain unquantified at the present time.

Epilepsy, other Neurological problems and Post traumatic stress disorder:

The efficacy of cannabis in treating neurological problems, including multiple sclerosis, epilepsy, and movement problems, is not clear. Studies of the efficacy of cannabis for treating multiple sclerosis have produced varying results. The combination of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) extracts give subjective relief of spasticity, though objective post-treatment assessments do not reveal significant changes. Evidence also suggests that oral cannabis extract is effective for reducing patient-centered measures of spasticity. A trial of cannabis is deemed to be a reasonable option if other treatments have not been effective. Its use for MS is approved in ten countries. A 2012 review found no problems with tolerance, abuse or addiction. There is tentative evidence that medical cannabis is effective at reducing posttraumatic stress disorder symptoms, but, as of 2015, there is insufficient evidence to confirm its effectiveness for this condition. A 2016 review in the New England Journal of Medicine said that although there was a lot of hype and anecdotes surrounding medical cannabis and epilepsy current data from studies in humans are extremely limited, and no conclusions can be drawn.

The mechanisms by which cannabis may be effective in the treatment of epilepsy remain unclear. Epidiolex, a cannabis-based product developed by GW Pharmaceuticals for experimental treatment of epilepsy, underwent stage-two trials in the US in 2014. Pair of phase 3 trials for Dravet syndrome and Lennox-Gastaut syndrome begun and concluded in 2015 with promising results on the the benefits of cannabis to the human system. They are also running a phase 2 study of non-psychoactive cannabidivarin. In 2014, the American Academy of Neurology reviewed all available findings levering the use of marijuana to treat brain diseases. The result was that the scientific evidence is weak that cannabis in any form serves as medicinal for curing or alleviating neurological disorders. To ease multiple sclerosis patients' stiffness, which may be accomplished by their taking cannabis extract by mouth or as a spray, there is support. The academy has published new guidelines on the use of marijuana pills and sprays in the treatment of multiple sclerosis. A 2005 review and meta-analysis said that bipolar disorder was not well-controlled by existing medications and that there were good pharmacological reasons for thinking cannabis had therapeutic potential, making it a good candidate for further study.

Glaucoma:
In 2009, the American Glaucoma Society noted that while cannabis can help lower intraocular pressure, it recommended against its use because of its side effects and short duration of action, coupled with a lack of evidence that its use alters the course of glaucoma. As of 2008 relatively little research had been done concerning therapeutic effects of cannabinoids on the eyes.

Tourette syndrome:
A 2007 review of the history of medical cannabis said cannabinoids showed potential therapeutic value in treating Tourette syndrome (TS). A 2005 review said that controlled research on treating TS with dronabinol showed the patients taking the pill had a beneficial response without serious adverse effects; a 2000 review said other studies had shown that cannabis has no effects on tics and increases the individual's inner tension. A 2009 Cochrane review examined the two controlled trials to date using cannabinoids of any preparation type for the treatment of tics or TS (Muller-Vahl 2002, and Muller-Vahl 2003). Both trials compared delta-9-THC; 28 patients were included in the two studies (8 individuals participated in both studies). Both studies reported a positive effect on tics, but "the improvements in tic frequency and severity were small and were only detected by some of the outcome measures. The sample size was small and a high number of individuals either dropped out of the study or were excluded. The original Muller-Vahl studies reported individuals who remained in the study; patients may drop out when adverse effects are too high or efficacy is not evident. The authors of the original studies acknowledged few significant results after Bonferroni correction.

Cannabinoid medication might be useful in the treatment of the symptoms in patients with TS, but the 2009 review found that the two relevant studies of cannibinoids in treating tics had attrition bias, and that there was not enough evidence to support the use of cannabinoids in treating tics and obsessive compulsive behaviour in people with Tourette's syndrome.

Anorexia Nervosa:
Cannabinoids have been proposed for the treatment of primary anorexia nervosa, but have no measurable beneficial effect. The authors of a 2003 paper argued that cannabinoids might have useful future clinical applications in treating digestive diseases. Laboratory experiments have shown that cannabinoids found in marijuana may have analgesic and anti-inflammatory effects.

Adjunct of Cancer Therapy:
Cannabinoids have been shown to exhibit some anti-cancer effects in laboratory experiments, although there has been little research into their use as a cancer treatment in people. Laboratory experiments have suggested that cannabis and cannabinoids have anti - carcinogenic and anti - tumor effects including a potential effect on breast- and lung-cancer cells. The National Cancer Institute reports that as of November 2013 there have been no clinical trials on the use of cannabis to treat cancer in people, and only one small study using delta-9-THC that reported potential anti - tumoral activity. While cannabis may have potential for refractory cancer pain, use as an antiemetic, and as an antitumor agent, much of the evidence comes from outdated or small studies, or animal experiments. A 2010 Cochrane review said that cannabinoids were probably effective in treating chemotherapy-induced nausea in children, but with a high side effect profile (mainly drowsiness, dizziness, altered moods, and increased appetite). Less common side effects were ocular problems, orthostatic hypotension, muscle twitching, pruritus, vagueness, hallucinations, lightheadedness and dry mouth.

HIV/AIDS:
Evidence is lacking for both efficacy and safety of cannabis and cannabinoids in treating patients with HIV/AIDS or for anorexia associated with AIDS. As of 2013, current studies suffer from effects of bias, small sample size, and lack of long-term data.

Pain:
Cannabis appears to be somewhat effective for the treatment of chronic pain, including pain caused by neuropathy and possibly that due to fibromyalgia and rheumatoid arthritis. A 2009 review states it was unclear if the benefits were greater than the risks while a 2011 review considered it generally safe for this use. In palliative care the use appears safer than that of opioids. A 2014 review found limited and weak evidence that smoked cannabis was effective for chronic non-cancer pain.
The review recommended that it be used for people for whom cannabinoids and other analgesics were not effective. A 2015 review found moderate quality evidence that cannabinoids were effective for chronic pain. A 2015 meta-analysis found that inhaled medical cannabis was effective in reducing neuropathic pain in the short term for one in

five to six patients. Another 2015 systematic review and meta-analysis found limited evidence that medical cannabis was effective for neuropathic pain when combined with traditional analgesics.

5.0 FINDINGS:

5.1 Adverse effect of Cannabis

There is insufficient data to draw strong conclusions about the safety of medical cannabis but typically, adverse effects of medical cannabis use are not serious. These include: tiredness, dizziness, cardiovascular and psychoactive effects. Tolerance to these effects develops over a period of days or weeks. The amount of cannabis normally used for medicinal purposes is not believed to cause any permanent cognitive impairment in adults, though long-term treatment in adolescents should be weighed carefully as they are more susceptible to these impairments. Withdrawal symptoms are rarely a problem with controlled medical administration of cannabinoids. The ability to drive vehicle or operating machinery may be impaired until a tolerance is developed. Although supporters of medical cannabis say that it is safe, further research is required to assess the long-term safety of its use.

Long-term effects of cannabis:

THC, the principal psychoactive constituent of the cannabis plant, has low toxicity while the LD50 (dose of THC needed to kill 50% of tested rodents) is high. Acute effects may include anxiety and panic, impaired attention, and memory (while intoxicated), an increased risk of psychotic symptoms, and possibly increased risk of accidents if a person drives a motor vehicle while intoxicated. Psychotic episodes are well-documented and typically resolve within minutes or hours. There have been few reports of symptoms lasting longer.

Effects of chronic use may include bronchitis, a cannabis dependence syndrome, and subtle impairments of attention and memory. These deficits persist while chronically intoxicated. There is little evidence that cognitive impairments persist in adult abstinent cannabis users. Compared to non-smokers, people who smoked cannabis regularly in adolescence exhibit reduced connectivity in specific brain regions associated with memory, learning, alertness, and executive function. One study suggested that sustained heavy, daily, adolescent onset cannabis use over decades is associated with a decline in IQ by age 38, with no effects found in those who initiated cannabis use later, or in those who ceased use earlier in adulthood. There has been a limited amount of studies that have looked at the effects of smoking cannabis on the respiratory system. Chronic heavy marijuana smoking is associated with coughing, production of sputum, wheezing, coughing, and other symptoms of chronic bronchitis. Regular cannabis use has not been shown to cause significant abnormalities in lung function.

Cannabis smoke contains thousands of organic and inorganic chemical compounds. This tar is chemically similar to that found in tobacco smoke and over fifty known carcinogens have been identified in cannabis smoke, including; nitrosamines, reactive aldehydes, and polycylic hydrocarbons, including benzapyrene. Light and moderate use of cannabis is not believed to increase risk of lung or upper airway cancer. Evidence for causing these cancers is mixed concerning heavy, long-term use. In general there are far lower risks of pulmonary complications for regular cannabis smokers when compared with those of tobacco. Combustion products are not present when using a vaporizer, consuming THC in pill form, or consuming cannabis foods. There is serious suspicion among cardiologists, spurring research but falling short of definitive proof, that cannabis use has the potential to contribute to cardiovascular disease. Cannabis is believed to be an aggravating factor in rare cases of arteritis, a serious condition that in some cases leads to amputation. 97% of case – reports on cannabis users also smoked tobacco, a formal association with cannabis could not be made. If cannabis arteritis turns out to be a distinct clinical entity, it might be the consequence of vasoconstrictor activity observed from delta-8-THC and delta-9-THC. Other serious cardiovascular events including myocardial infarction, stroke, sudden cardiac death, and cardiomyopathy have been reported to be temporally associated with cannabis use. Research in these events is complicated because cannabis is often used in conjunction with tobacco, and drugs such as alcohol and cocaine. These putative effects can be taken in context of a wide range of cardiovascular phenomena regulated by the endocannabinoid system and an overall role of cannabis in causing decreased peripheral resistance and increased cardiac output, which potentially could pose a threat. A 2008 German review reported that cannabis was a causal factor in some cases of schizophrenia and stressed the need for better education among the public due to increasingly relaxed access to cannabis. A 2008 National Institutes of Health study of 19 chronic heavy marijuana users with cardiac and cerebral abnormalities (averaging 28 g to 272 g (1 to 9+ oz) weekly) and 24 controls found elevated levels of apolipoprotein C-III (apoC-III) in the chronic smokers. An increase in apoC-III levels induces the development of hypertriglyceridemia.

Short-Term Side Effects:

Medical marijuana can change your mood, making you feel happy, relaxed, sleepy, or anxious. It can also disrupt your short-term memory and decision-making ability. These side effects can last 1 to 3 hours. Large doses of medical

marijuana can make some people have hallucinations, delusions, and paranoia. Research suggests that smoking marijuana can make breathing problems, like bronchitis, worse.

Why isn't the marijuana plant an FDA-approved medicine?

The FDA requires carefully conducted studies (clinical trials) in hundreds to thousands of human subjects to determine the benefits and risks of a possible medication.

So far, researchers have not conducted enough large-scale clinical trials that show that the benefits of the marijuana plant (as opposed to its cannabinoid ingredients) outweigh its risks in patients it is meant to treat.

What are cannabinoids?

Cannabinoids are chemicals related to delta-9-tetrahydrocannabinol (THC), marijuana's main mind-altering ingredient. Other than THC, the marijuana plant contains more than 100 other cannabinoids. Scientists as well as illegal manufacturers have produced many cannabinoids in the lab. Some of these cannabinoids are extremely powerful and have led to serious health effects when abused.

The body also produces its own cannabinoid chemicals. They play a role in regulating pleasure, memory, thinking, concentration, body movement, awareness of time, appetite, pain, and the senses (taste, touch, smell, hearing, and sight).

What is CBD?

There is growing interest in the marijuana chemical cannabidiol (CBD) to treat certain conditions such as childhood epilepsy, a disorder that causes a child to have violent seizures. Therefore, scientists have been specially breeding marijuana plants and making CBD in oil form for treatment purposes. These drugs may be less desirable to recreational users because they are not intoxicating.

How might cannabinoids be useful as medicine?

Currently, the two main cannabinoids from the marijuana plant that are of medical interest are THC and CBD. THC increases appetite and reduces nausea. The FDA-approved THC-based medications are used for these purposes. THC may also decrease pain, inflammation (swelling and redness), and muscle control problems. CBD is a cannabinoid that does not affect the mind or behavior. It may be useful in reducing pain and inflammation, controlling epileptic seizures, and possibly even treating mental illness and addictions. NIH-funded and other researchers are continuing to explore the possible uses of THC, CBD, and other cannabinoids for medical treatment.For instance, recent animal studies have shown that marijuana extracts may help kill certain cancer cells and reduce the size of others. Evidence from one cell culture study suggests that purified extracts from whole-plant marijuana can slow the growth of cancer cells from one of the most serious types of brain tumors. Research in mice showed that treatment with purified extracts of THC and CBD, when used with radiation, increased the cancer-killing effects of the radiation (Scott, 2014).

Are People with Health- and Age-Related Problems More Vulnerable to Marijuana's Risks?

Regular medicinal use of marijuana is a fairly new practice. For that reason, its effects on people who are weakened because of age or illness are still relatively unknown. Older people and those suffering from diseases such as cancer or AIDS could be more vulnerable to the drug's harmful effects. Scientists need to conduct more research to determine if this is the case.

What medications contain cannabinoids?

Two FDA-approved drugs, dronabinol and nabilone, contain THC. They treat nausea caused by chemotherapy and increase appetite in patients with extreme weight loss caused by AIDS.

The United Kingdom, Canada, and several European countries have approved nabiximols (Sativex), a mouth spray containing THC and CBD. It treats muscle control problems caused by MS. The United States is conducting clinical trials for its safe use in treating cancer pain. Although it has not yet undergone clinical trials, scientists have recently created Epidiolex, a CBD-based liquid drug to treat certain forms of childhood epilepsy.

6.0 RESULTS:

6.1 Medical Physiology of Cannabis

Cannabis is usually smoked as a joint, a variable mixture of hashish (or marijuana) and tobacco. The dosage depends on the desired effect (generally one cigarette containing2 percent THC). The active principle is absorbed very rapidly via the respiratory tract, lungs, with an onset of action just a few minutes later. The effect peaks at fifteen minutes, subsides gradually after thirty to sixty minutes, and is largely finished after two to three hours. The bioavailability (proportion of substance active in the body) depends greatly on the smoker's technique and varies between 10 and 25 percent (with a maximum of 56 percent). THC is absorbed by the body much more slowly after oral intake (eating or

drinking) and then has a lower bioavailability of 4 to 12 percent because of the poorer absorption, catabolism (breakdown into simpler substances) in the liver, and the fact that the inactive tetrahydrocannabinolidic acids in natural cannabis products cannot be transformed into psychoactive delta-9-THC unless they are heated first, as is the case when they are smoked. In contrast to absorption through the respiratory tract, in which peak plasma concentrations of THC may be achieved while the product is being smoked, the plasma concentration increases constantly over a period of four to six hours when cannabis is ingested; a state of intoxication is reached later and is of a different quality. The high solubility of delta-9-THC and its active metabolite 11-OH-delta-9-THC in fat mean that they are bound almost completely to protein in the plasma, cross the blood brain barrier with ease, and are eliminated only slowly from lipid-containing tissue. This slow elimination gives the substances a biological half-life of one day; other authors have reported half-lives of three to five days. The substances are thought to be metabolized twice as quickly by chronic users of cannabis as by first-time users. The cannabinoids are metabolized rapidly in the liver. To date, some 80 different, mostly inactive metabolites have been identified. No major metabolic differences between male and female users of cannabis have been observed.

There are several pharmacokinetic aspects of THC that have an impact on the effects of cannabis, but these are frequently misunderstood. THC is metabolized to the active metabolite 11-OH-delta-9-THC, but this is unlikely to contribute to THC's pharmacological effects because it is converted to the corresponding active metabolite, which is inactive. It is this latter metabolite that serves as the primary urinary marker for detecting cannabis use. It has been shown that THC can be deposited in fatty tissues for long periods of time after use. However, there is no evidence that THC exerts a deleterious effect when deposited in tissue or during its slow egress from these sites.Although the primary psychoactive effects of cannabis are attributed to THC, there is no linear relationship between blood levels and pharmacological effects with respect to time, a situation that hampers the prediction of cannabis-induced impairment based on THC blood levels. Immediately following cannabis smoking, high concentrations of delta-9-THC are present in the blood and distributed to the tissues.

The physiological and psychic effects of cannabis increase during this distribution phase, but may peak at times when blood concentrations of delta-9-THC are falling. Once equilibrium is established between brain and blood concentrations (approximately forty-five minutes after use), a linear relationship between blood concentrations and pharmacological effects appears. Recently developed mathematical models are useful in interpreting the relationship of delta-9-THC and metabolite concentrations in blood to drug-induced effects and in estimating time elapsed since cannabis use.

6.2 Pharmacodynamics

As mentioned above, specific research into the mode of action of cannabis was notpossible until 1964, when delta-9-THC was isolated and its structure was elucidated. It then became possible to develop substances with an action similar to THC, some of them highly potent. During the 1980s, various scientific findings removed any lingering doubt about the existence of specific cannabis receptors.A cannabinoid receptor (CB1) located predominantly in the cerebellum, the hippocampus and the cerebral cortex was finally discovered and cloned in 1990. A further, peripheral, receptor (CB2) was found in certain parts of the immune system (e.g. the spleen) in 1993. Investigations carried out to date would seem to confirm that these receptors are capable of affecting neurophysiological processes in the brain. Future research will reveal the extent to which processes of this type involving cannabinoid receptors are linked to the complex effects of cannabis in humans. In 1992, the endogenous ligand (linking substance) anandamide was discovered; it is thought to be synthesized and released on an ad hoc basis. The discovery of the cannabinoid receptors, endogenous ligands, and the development of specific agonists and antagonists in the past and the future, are making a major contribution to scientific understanding of the effects of cannabis, of the neurophysiological role played by thesereceptors, and of the possible effects on the human brain and its functions in the context of chronic cannabis use. New knowledge will perhaps enable the development of an active principle which is therapeutically highly active but has none of the psychoactive properties.

6.3 Acute effects of cannabis

The acute effects of cannabis use are an altered state of consciousness characterized by mild euphoria and relaxation, perceptual alterations, including time distortion, and the intensification of ordinary sensory experiences, such as those associated with eating, watching films and listening to music. When used in a social setting its effects may include infectious laughter and loquacity. There are also pronounced cognitive effects, such as impaired short-term memory and a loosening of associations, enabling the user to become lost in pleasant reverie and fantasy. Motor skills and reaction time are also impaired so that skilled activity of various kinds is frequently disrupted.

6.4 Acute effects of cannabis on the central nervous system

The psychotropic (affecting the central nervous system and the mind) action of cannabis is one of the reasons why cannabis products are used so widely. As mentioned above,cannabis starts to act more rapidly and more intensively when it is smoked, and the intoxication lasts a shorter time than when it is absorbed through the digestive system. The effect of cannabis depends not only on its composition, dosage and mode of consumption; much also depends on the mood of the individual, on the individual's expectations, and on the atmosphere and setting. These factors explain why the altered state of consciousness, which may amount to pronounced intoxication, is experienced so differently by different people. At a low to moderate dose, cannabis produces a largely pleasant feeling of relaxed euphoria, perhaps even with dreamy elements, which may be accompanied by heightening or alteration of the senses. The sense of time shiftsmarkedly, and the individual perceives periods of time as being considerably longer thanthey really are. Short-term memory is impaired35, although recall of previously acquired knowledge is impaired only slightly if at all. It is uncertain whether other higher functions of the brain, such as the organization and integration of complex information, are affected. Higher doses produce a general reduction in spontaneity, drive and involvement in the surroundings. Anxiety, confusion, aggressive feelings, (pseudo) hallucinations, nausea and vomiting have all been reported but are not usually experienced. They may, however, develop even in experienced users. As the effects of THC subside, the individual often becomes drowsy and tired, but there is no "hangover" comparable to the effect experienced after heavy alcohol consumption.

6.5 Acute side effects and toxicity of cannabis

The physiological effects observed immediately after consumption are reddening of the conjunctivae of the eyes, a reduction in body temperature, a dry mouth and throat, hunger, a slightly elevated heart rate and blood pressure when lying down, and a drop in heart rate and blood pressure when standing.Heart rate may increase 20 to 50 percent over baseline. This tachycardia occurs within a few minutes to a quarter of an hour and can last up to three hours.

In healthy young users these cardiovascular effects are unlikely to be of any clinical significance because tolerance develops to the effects of THC, and young healthy hearts will be only mildly stressed. The acute toxicity of cannabis is generally thought to be low. If the dose of cannabis lethal in rhesus monkeys is extrapolated to man, a human would have to smoke one hundred grams of hashish to achieve the same effect. No human fatality has ever been reported in the world medical literature in connection with acute cannabis intoxication. The lethal dose also increases as one move up the phylogenetic/evolutionary tree, suggesting by extrapolation that the lethal dose in humans could not be easily achieved by smoking or ingesting the drug. This feature distinguishes cannabis from other drugs of abuse in that almost all can produce lethality at high doses. Unfortunately, this fact is often used to portray cannabis as a safe drug, an implication that cannabis can be used without adverse effects. In actual fact, most problems stemming from cannabis abuse can be attributed to disruption of a normal productive life rather than death. Use of high-dose cannabis products can lead to psychotic states which manifest as a combination of emotional symptoms, such as fluctuating mood, disorientation and schizophrenia-like states, as well as depression, anxiety, visual and auditory hallucinations, and paranoid persecution mania. Panic reactions are often due to the individual's fear of losing his or her life. The treatment of such states often involves nothing more than reassuring the person. Drug therapy is generally unnecessary because the calming effect of the drug in any case comes to the fore as the intoxication subsides. When evaluating the significance of the potential negative effects of cannabis consumption mentioned above, it should not be forgotten that similar effects may also occur in patients using many of the psychoactive medications prescribed today. A number of studies have attempted to correlate plasma concentrations of delta-9-THC and its metabolites with the psychoactive effects of cannabis in order to deduce the extent of the intoxicated state currently being experienced by an individual, or to determine when cannabis was last used. However, this is far more difficult than with alcohol because of the many factors that affect the pharmacological action of cannabis. Peakplasma concentrations do not correspond to the point of maximum intoxication whencannabis is inhaled (smoked), injected intravenously or ingested (eaten or drunk). More recent mathematical models are thought to permit more accurate assessment of the time that has elapsed since cannabis was last consumed.

6.6 Psychological Effects of Cannabis (Effects on Human Behaviour and Central Nervous System Functions)

Cannabis and the Brain

Employing modern brain imaging technologies, such as the CAT scan, magnetic resonance imaging (MRI), electro encephalogram (EEG)etc ,researchers havefound no evidence of brain damage in human cannabis users, even in subjectssmoking an average of nine cannabis cigarettes per day. Brain wave patterns of chroniccannabis users and non-users, produced by standard electroencephalographic (EEG) tests cannot be distinguished by visual examination. Using computer-generated quantitativeanalysis, however, one group found differences in the distribution of certain brainwavefrequencies between heavy cannabis users and occasional users - differences of unknown significance.

Using a specialized EEG technique, researchers have also measured the amplitude of a particular brain wave (the P300) in response to auditory and visual stimuli. One study found minor abnormalities in this event-related potential (ERP) of chronic cannabis users. However, in the only ERP study to use medically and psychiatrically healthy

subjects, and to institute controls for age, researchers found no difference in the ERP responses on chronic cannabis users and non - users.

Cognitive Effects:

The available evidence suggests that even long-term heavy use of cannabis produces nosevere or grossly debilitating impairment of cognitive function. There is noevidence, for example, that it produces anything comparable to the cognitive impairments found in chronic heavy alcohol drinkers; if it did, research to date should have detected it. There is some clinical and experimental evidence, however, that the long-term use of cannabis may produce more subtle cognitive impairment in the higher cognitive functions of memory, attention and organization, and the integration of complex information. The evidence suggests that the longer the period of cannabis use, the more pronounced the cognitive impairment. It remains to be determined how significant these impairments are for everyday functioning and whether they are reversed after an extended period of abstinence from cannabis. A suspicion that chronic heavy cannabis use may cause gross structural brain damage was raised by a single poorly controlled study which reported that cannabis users had enlarged cerebral ventricles. Since then a number of better controlled studies using more sophisticated methods of investigation have consistently failed to provide evidence of structural change in the brains of heavy long-term cannabis users. These negative results are consistent with the evidence that any cognitive effects of chronic cannabis use are subtle and hence unlikely to be manifested as gross structural changes in the brain.

Although experimental studies have identified many effects of cannabis administration, it is difficult to predict how and to what degree these effects could disrupt real-life functioning, especially in naive users. Previous experience with cannabis could possibly attenuate its acute effects through a variety of tolerance mechanisms, or might even result in an exaggerated response, relative to a naive user, through accumulated toxicity. Although the use of cannabis-naive subjects is experimentally desirable, it often may not be allowed for ethical reasons. A variety of non-pharmacological factors can modulate the effects of cannabis and these factors are often uncontrolled, unreported or non-standardized across experimental studies. The subject's personality and attitude toward cannabis, experience with tasks similar to the experimental tasks, variations in the physical environment, and the consequences (e.g. rewards) for completing the experimental tasks correctly vary from study to study.

The existence of a naturally occurring cannabinoid-like substance in the human brain (anandamide) signifies that this substance plays some role in our normal functioning. It has been suggested that anandamide may play a role in movement or motor control, in sleep, and in the modulation of attention. Although substantial research on the psychomotor and cognitive effects of cannabis has resulted in a greater awareness of the functional effects of cannabis consumption, the mechanisms through which these functional effects are produced remain largely obscure. Additional research on the mechanisms through which cannabis alters behaviour is necessary.

Effects of Cannabis on Memory:

Although several studies before and after 1981 have documented that cannabis can affect memory, the effects are typically modest, at least in comparison to effects reported with other behaviorally active drugs. Free recall, where items-to-be-learned and their recall occur with cannabis present, is often impaired, and the major impairment is often in intrusions of new items. The few studies evaluating the recall of prose material have generally reported deleterious effects induced by cannabis. Effects of cannabis on recognition and paired-associate tasks have, however, been inconsistent. Typically, once something is learned, recall is little impaired by cannabis if cannabis is present only during recall. Although the effects of cannabis on memory appear to be modest, it is unclear to what degree the level of difficulty of the memory task determines the magnitude of the effect imposed by cannabis. Few studies have been conducted to manipulate this variable across cannabis-dosing conditions. It is also unclear how the consequences of performance could modulate the effects of cannabis on performance, e.g. could increase monetary reward produce corresponding decreases in detriments imposed by cannabis. Earlier reviews have suggested that the consequences of performance can indeed modulate the effects of cannabis, but this variable seems to have been largely ignored in recent years.

During the past thirty years, researchers have found, at most, minor cognitive differences between chronic cannabis users and non-users, and the results differ substantially from one study to another. Based on this evidence, it does not appear that long-term cannabis use causes any significant permanent harm to intellectual ability. Even animal studies, which show short-term memory and learning impairment with high doses of THC, have not produced evidence of permanent damage. It has been suggested by S.A. Deadwyler that endogenous cannabinoids (those originating within the brain) are involved in the selective forgetting or elimination of certain information at the encoding stage of short-term memory, and that exogenous cannabinoids (e.g, THC) override the normal function of the endogenous cannabinoids by disrupting the encoding of information when it is not appropriate or advantageous to do so. The

neurotransmitters and peptides that govern ourbehaviour are finely balanced and any surplus or depletion generally results in dysfunction. With long-term use of cannabis, prolonged or continual binding to the cannabinoid receptor may alter its properties also in the long term. These physiological mechanisms and the interactions between ingested cannabis, ananamide and the cannabinoid receptor need to be elucidated. There is converging evidence that dysfunction due to chronic cannabis use lies in the realm of the higher cognitive functions that appear to be sub served by the frontal lobes; these are important in organizing, manipulating and integrating a variety of information, and in structuring and segregating events in memory.

Effects of Cannabis on Appetite:

In preliminary studies by Foltrin and colleagues on the effects of smoking cannabis on food intake, where subjects lived in a residential laboratory and engaged in structured work activities as well as social activities, analysis of the data indicated that increases in food intake were attributable to increases in eating occasions and were confined to the social-access periods and to the consumption of snacks. The authors speculated that the interactive social effects may have played a part in the food consumption increases observed. In a follow-up study by Foltrin and colleagues, subjects smoked placebo or active cannabis twice a day in their private rooms and twice a day in their social areas. Smoking active cannabis cigarettes increased food intake during both the private and social periods. The greatest rate of change in caloric intake occurred during the social periods for most subjects. Smoking cannabis cigarettes nearly doubled the number of snack occasions during both the private and social periods without affecting the number of meal occasions, and the increases in caloric intake were mainly attributable to these snack occasions. The authors concluded that it was most likely a dose effect rather than a social effect that restricted the increases of food consumption to the social periods of their original study. Although there have been several studies reporting that cannabis increases the intake of food, there have been fewer and less consistent reports that have documented that "appetite," the individual's self-report of the current level of hunger is similarly increased. It is difficult to determine whether there is truly dissociation between cannabis-increased consumption of food and levels of self-reported hunger ratings because few studies have explicitly assessed both variables.

Amotivational Syndrome:

Acute, reversible psychotic states have been documented in exceptional cases following cannabis use, but the existence of amotivational syndrome, first described in the literature in 1968, has never been confirmed. The term was used to describe the changes in attitude and personality, the neglect of appearance, and general disinterest displayed by chronic users of cannabis, although nowadays it is considered to be obsolete and not typical of cannabis consumption. It is exceptionally difficult if not impossible to establish a direct and exclusive causality between speculative consequences of chronic cannabis use and the drug itself. For example, studies attempting to link dropping out of school at an early age with cannabis use have tended to show that it was in fact the family background, the child's relationship with parents during the school years, social values, etc. which led the child to stop going to school. The evidence for amotivational syndrome amongadults consists largely of case histories and observational reports.

The few controlled field and laboratory studies have not found compelling evidence for such a syndrome. The value of the negative field studies is limited by their small sample sizes and the limited socio - demographic characteristics of their samples, while the evidential value of the laboratory studies is limited by the short periods of drug use, the youth and good health of the volunteers, and the minimal demands made on the motivation of volunteers in the laboratory.

There has been limited supportive evidence for the occurrence of an amotivationalsyndrome among adolescents. Cannabis use appears to increase the risk of discontinuing a high-school education and of experiencing job instability in young adulthood. The apparent strength of these relationships in cross-sectional studies may have been exaggerated because those adolescents who are most likely to use cannabis have lower academic aspirations and poorer high school performance prior to using cannabis than their peers who do not. There is suggestive evidence that heavy cannabis use has adverse effects upon family formation, mental health and involvement in drug-related crime. In each case, however, the apparently strong associations revealed in cross-sectional data are much more modest in longitudinal studies after statistically controlling for associations between cannabis use and other pre-existing characteristics that independently predict theseadverse outcomes.

Canadian researchers designed a token-economy study (where subjects worked for tokens which could be exchanged for cannabis) to evaluate cannabis' impact on motivation. They found that subjects worked less efficiently in the period immediately after they were allowed to smoke cannabis. However, productivity quickly increased and surpassed levels achieved during the abstinence period. Although subjects consuming the most cannabis spent the least amount of time working, overall, they were no less productive. This was because when they worked, they worked harder. In addition, during the period of highest cannabis consumption, subjects organized a strike and successfully negotiated with researchers for increased wages.

Dependence and Tolerance:

Cannabis consumption can lead to psychological dependence; it is estimated that around half of heavy users develop dependence of this type237. In a German study, one in five respondents admitted to frequently or very frequently consuming more cannabis than they had intended. The tendency to develop physical dependence is only weak. It has been demonstrated in animal experiments by administering an antidote (the receptor antagonist SR 141716A) following chronic administration of cannabis and observing withdrawal symptoms. Abrupt withdrawal in humans following heavy daily consumption produces autonomic withdrawal symptoms such as nausea, perspiration, trembling, insomnia, and loss of appetite. These symptoms regress following renewed administration of cannabis, an observation that corroborates the development of dependence. The dependence profile is classified by the World Health Organization as a distinctive type of dependence, known as cannabis-type dependence.

The development of tolerance is associated with pharmaco - dynamic changes. Chronic administration of THC has been shown to reduce the number of receptor binding sites, although this appears to be reversible. The tolerance to the functional and psychological effects of THC observed in animal experiments has also been demonstrated in man, but does not lead the individual to increase the dose of cannabis. Clear tolerance development has been demonstrated with respect to mood swings, elevated heart rate, and impairment of psychomotor functions. The conditions under which tolerance and dependence develop high doses of THC over a long period do not correspond to the widespread recreational use of cannabis, and this is why these properties of cannabis may not necessarily constitute a serious problem. The existence of a cannabis dependence syndrome among some heavy and long-term cannabis users can be inferred from data on the prevalence and characteristics of persons seeking professional help to stop using cannabis, from observational studies of problems reported by non-treatment samples of long-term cannabis users, and from clinical research on the validity of the cannabis dependence syndrome as embodied in the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, (DSM-III-R) (American Psychiatric Association 1987) and other classification systems. Direct support for the validity of a cannabis dependence syndrome comes from studies of diagnostic criteria for substance dependence. Kosten et al tested the extent to which the DSM-III-R psychoactive substance dependence disorders for alcohol, cannabis, cocaine, hallucinogens, opioids, sedatives, and stimulants constituted syndromes. There was consistent support for a unidimensional dependence syndrome for alcohol, cocaine and opiates.The results were more equivocal in the case of cannabis. A Principal Components Analysis (PCA) suggested that there were three dimensions of cannabis dependence: (1) compulsion – indicated by impaired social activity attributable to drug use, preoccupation with drug use, giving up other interests, and using more than intended; (2) inability to stop – indicated by inability to cut down, rapid reinstatement after abstinence, and tolerance to drug effects; and (3) withdrawal – identified by withdrawal symptoms, use of cannabis to relieve withdrawal symptoms, and continued use despite problems.

Psychotic Disorders:

There is suggestive evidence that large doses of THC can produce an acute psychosis in which confusion, amnesia, delusions, hallucinations, anxiety, agitation, and hypomanic (mild mania without much change in behaviour) symptoms predominate. The main evidence comes from clinical observations of psychotic symptoms in heavy cannabis users that occur after unusually heavy cannabis use, appear to comprise a syndrome, and remit rapidly after abstinence from cannabis253. Epidemiological research has produced reasonably consistent evidence from case-control, cross-sectional and prospective studies that there is an association between cannabis use and schizophrenia. The prospective study of Andreasson et al, showed a dose-response relationship between the frequencies with which cannabis had been used by age eighteen and the risks over the subsequent fifteen years of being diagnosed as schizophrenic. This relationship has been interpreted by some as evidence that chronic cannabis use may precipitate schizophrenia in vulnerable individuals.Others are more sceptical.

They note that in the only prospective study conducted to date, the use of cannabis was not documented at the time of diagnosis, there was a possibility that cannabis use was confounded by amphetamine and other drug use, and there were doubts about whether the study could reliably distinguish between schizophrenia and acute psychoses induced by cannabis or other drugs. Even if this relationship is a causal one, its public health significance should not be overstated. The findings of Andreasson et al. indicate that fewer than 10 percent of cases of schizophrenia are attributable to cannabis use. On the grounds of biological plausibility it is probable that cannabis use exacerbates the symptoms of schizophrenia and precipitates schizophrenic disorders. However, the declining incidence of treated cases makes it unlikely that cannabis use has caused schizophrenia that would not otherwise have occurred.

7.0 RECOMMENDATION:

Adequate and well-controlled studies of smoked marijuana should be conducted in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy, including AIDS wasting syndrome, severe acute or delayed emesis induced by chemotherapy, multiple sclerosis, spinal cord injury, dystonia, and neuropathic pain.

Research on the clinical indications for medical prescription of cannabinoids should be undertaken. For all indications listed below (antiemetics, pain, epilepsy, glaucoma, asthma, immunological effects, multiple sclerosis, spinal cord injury, and other spastic disorders) further research is required to establish suitable methods of administration, optimal dosage regimens, and routes of administration. A central registry should be kept of patients prescribed cannabinoids so that the effects can be followed up over the long term. For at least some potential indications, marijuana looks promising enough to recommend that new controlled studies be done.

The indications in which varying levels of interest were expressed are the following: appetite stimulation and wasting, chemotherapy-induced nausea and vomiting, neurological and movement disorders, analgesia and glaucoma. Until studies are done using scientifically acceptable clinical trial design and subjected to appropriate statistical analysis, the question concerning the therapeutic utility of marijuana will likely remain largely un-answered.
Therapeutic uses of cannabinoids warrant further basic pharmacological and experimental investigation and clinical research into their effectiveness. More research is needed on the basic neuropharmacology of THC and other cannabinoids so that better therapeutic agents can be found.

8.0 CONCLUSION:
Until better measures have been developed to investigate the subtleties of dysfunction produced by chronic cannabis use, cannabis can be viewed as posing a lower level threat to cognitive function than other psychoactive substances such as alcohol.

REFERENCES:

1. National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services
2. Scott KA, Dalgleish AG, Liu WM. The combination of cannabidiol and Δ9-tetrahydrocannabinol enhances the anticancer effects of radiation in an orthotopic murine glioma model. Mol Cancer Ther. 2014;13(12):2955-67.
3. M.E. Wall, B.M. Sadler et al., Metabolism, disposition and kinetics of delta-9-THC in men and women, Clin. Pharmacol.Ther.34 (3), 352-363, 1983.
4. D.S. Kreuz and J. Axelrod, Delta-9-THC: Localization in body fat, Science, vol. 1979, 1973, 391 and 392.
5. E. Joansson and others, Prolonged apparent half-life of delta-9-THC in plasma of chronic marijuana users, Journal of Pharmacy and Pharmacology, vol. 40, 1988, 374 and 375.
6. M.A. Huestis, J.E. Henningfield and E.J. Cone, Blood cannabinoids. II. Models for the prediction of time of marijuana exposure from plasma concentrations of delta-9-THC and 11 –nor-9-carboxy -delta-9-THC (THCCOOH), Journal of Analytical Toxicology, vol. 16, 1992, 283-290.
7. P.M. O'Malley, J.G. Bachman, L.D. Johnston, Reliability and consistency of self-reports of drug use, International Journal of the Addictions 18: 805-824, 1983.
8. Health Council of the Netherlands, Standing Committee on Medicine. 1996. Marihuana as Medicine. Rijswikj, the Netherlands: Health Council of the Netherlands.
9. Report of the Council on Scientific Affairs. 1997. Report to the American Medical Association House of Delegates. Subject: Medical Marijuana. Chicago: AMA.
10. British Medical Association. 1997. Therapeutic Uses of Cannabis. United Kingdom: Harwood Academic Publishers.
11. National Institutes of Health. 1997. Workshop on the Medical Utility of Marijuana. Bethesda, MD: National Institutes of Health.
12. World Health Organization 1997: Cannabis: A Health Perspective and Research Agenda. Geneva: WHO.
13. W. Hall, L. Johnston, N. Donnelly, Epidemiology of cannabis use and its consequences, The Health Effects of Cannabis, Addiction Research Foundation, 1999.
14. M. Bidaut-Russel, W.A. Devane et al., Cannabinoid receptors and modulation of cyclic AMP accumulation in the rat brain, 55, 21-26, 1990.
15. W.L. Dewey, B.R. Martin et al., Cannabinoid stereoisomers: Pharmacological effects, 317-326, 1984, in
16. D.F. Smith (ed.), Handbook of Stereoisomers: Drugs in Psychopharmacology, CRC Press, Boca Raton.
17. A.C. Howlett and R.M. Fleming, Cannabinoid inhibition of adenylatecyclase: pharmacology of the response in neuroblastoma cell membranes, Mol. Pharmacol. 26, 532-538, 1984.
18. A.C. Howlett, J.M. Qualy et al., Involvement of Gi in the inhibition of adenylatecyclase by cannabimimetic drugs, Mol. Pharmacol. 29, 307-313, 1986.
19. M.E. Abood and B.R. Martin, Molecular neurobiology of the cannabinoid receptor, Int. Rev. Neurobiol39, 1996.
20. J. Axelrod and C.C. Felder, Cannabinoid receptors and their endogenous agonist, anandamide, Neurochem. Res. 23 (5), 575-581, 1998.
21. M.O. Maykut, Health Consequences of acute and chronic marijuana use, Prog.NeuroPhychopharmacol, and Biol. Psychiat. 9 (3), 209-238, 1985.
22. S. Agurell, M. Halldin et al., Pharmacokinetics and metabolism of delta-9-THC and other cannabinoids with emphasis on man, Pharm. Rev. 38 (1), 21-43, 1986.

23. G. Edwards, Cannabis and the psychiatric position, in Cannabis and Health, J.D.P. Graham (ed.) London, Academic Press, 1976.
24. S. Andeasson and others, Cannabis and schizophrenia: A longitudinal study of Swedish conscripts, The Lancet, vol. 1, 1483-1485, 1987
25. http://www.webmd.com/brain/ss/slideshow-medical-marijuana
26. http://www.mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/medical-marijuana/art-20137855?pg=1 and 2
27. https://www.ncbi.nlm.nih.gov/books/NBK230707/
28. R.W. Foltrin, M.W. Fischman and M.F. Byrne, Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory, Appetite 11, 1-14, 1988.
29. Murnion, B (December 2015) : Medicinal cannabis. Australian prescriber. 38 (6): 212–5. doi:10.18773/austprescr.2015.072. PMC 4674028Freely accessible.PMID 26843715.
30. J. Kuehnle et al, Computed tomographic examination of heavy marijuana smokers, Journal of American Medical Association 237, 1977.
31. J. Hannerz and T. Hindmarsh, Neurological and Neuroradiological Examination of Chronic Cannabis Smokers, Annals of Neurology 13, 207-210, 1983.
32. F.A Struve and J.J. Straumanis, Electroencephalographic and evoked potential methods in human marijuana research: Historical review and future trends, Drug Development Research 20, 369-388, 1990.
33. F.A. Struve et al., Persistent topographic quantitative EEG sequelae of chronic marijuana use: A replication study and initial discriminant function analysis, Clinical Electroencephalography 25, 63-73,
34. G. Patrick et al., Auditory and visual P-300 event-related potentials are not altered in medically and psychiatrically normal chronic marijuana users, Life Sciences 56, 2135-2140, 1995.
35. W.E. Carter, W. Coggins and P.L. Doughty, Cannabis in Costa Rica: a study of chronic marijuana use, Philadelphia, Institute for the Study of Human Issues, 1980.
36. K.O. Fehr and H. Kalant, Long-term effects of cannabis on cerebral function: A review of the clinical and experimental literature, in Cannabis and Health Hazards, K.O. Fehr and H. Kalant (eds.), Toronto, Addiction Research Foundation, 501-576, 1983.
37. N. Solowij et al., Effects of long-term cannabis use on selective attention: An event-related potential study, Pharmacology, Biochemistry and Behaviour 40, 683-688, 1991
38. What is medical marijuana : National Institute of Drug Abuse. July 2015. Retrieved 19 April 2016.
39. Release the strains :Nature Medicine. 21: 963. 4 September 2015. doi:10.1038/nm.3946. Retrieved 8 September 2015.
40. Borgelt, LM; Franson, KL; Nussbaum, AM; Wang, GS (February 2013). The pharmacologic and clinical effects of medical cannabis.Pharmacotherapy. 33 (2): 195–209. doi:10.1002/phar.1187. PMID 23386598.
41. Jensen, Bjorn; Chen, Jeffrey; Furnish, Tim; Wallace, Mark (1 September 2015). Medical Marijuana and Chronic Pain: a Review of Basic Science and Clinical Evidence. Current Pain and Headache Reports.19 (10).doi:10.1007/s11916-015-0524-x.
42. Ben Amar M (2006) :Cannabinoids in medicine: a review of their therapeutic potential PDF). Journal of Ethnopharmacology (Review). 105 (1–2): 1–25. doi:10.1016/j.jep.2006.02.001. PMID 16540272.
43. American Medical Association Reaffirms Opposition to Marijuana Legalization.Retrieved 25 April 2014.
44. American Society of Addiction Medicine Rejects Use of 'Medical Marijuana. Retrieved 25 April 2014.
45. Minnesota doctors oppose medical marijuana bill. Retrieved 25 April 2014.
46. American Academy of Pediatrics Reaffirms Opposition to Legalizing Marijuana for Recreational or Medical Use. American Academy of Pediatrics. 26 January 2015. Retrieved 28 January 2015.
47. H-95.952 Cannabis for Medicinal Use.American Medical Association.Retrieved 24 June 2015.
48. Australia to give green light to medical cannabis - CNN.com.CNN.Retrieved 17 October 2015.
49. Federal Government to legalise growing of medicinal cannabis. ABC News.Retrieved 17 October 2015.
50. Bob Egelko (15 January 2014). "Court upholds crackdown on pot dispensaries". SFGate. Hearst Communications, Inc. Retrieved 3 March 2014.
51. Consumer Reports (28 April 2016). Up in Smoke: Does Medical Marijuana Work.Consumer Reports.Retrieved 24 May 2016.
52. Schubart CD, Sommer IE, Fusar-Poli P, de Witte L, Kahn RS, Boks MP (2014). Cannabidiol as a potential treatment for psychosis (PDF).European Neuropsychopharmacology. 24 (1): 51–64. doi:10.1016/j.euroneuro.2013.11.002. PMID 24309088.
53. Barbara S. Koppel, MD, FAAN, John C.M. Brust, MD, FAAN, Terry Fife, MD, FAAN, Jeff Bronstein, MD, PhD, Sarah Youssof, MD, Gary Gronseth, MD, FAAN, and David Gloss, MD (2014). "Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders". Neurology. 82 (17): 1556–1563. doi:10.1212/WNL.0000000000000363. PMC 4011465Freely accessible.PMID 24778283.
54. Sachs J, McGlade E, Yurgelun-Todd D (2015). Safety and Toxicology of Cannabinoids.Neurotherapeutics. 12 (4): 735–746. doi:10.1007/s13311-015-0380-8. PMC 4604177Freely accessible.PMID 26269228.
55. Arseneault L, Cannon M, Witton J, Murray RM (2004).Causal association between cannabis and psychosis: examination of the evidence. The British Journal of Psychiatry. 184 (2): 110–117. doi:10.1192/bjp.184.2.110. PMID 14754822.