IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A BRIEF DISCUSSION ABOUT MARIJUANA AS A PHYTOMEDICINE

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Abstract

This literature review paper is developed as a part of the awareness and to gather scientific information about the medicinal plant, Cannabis sativa. Several researches have shown the potential medicinal activity of Cannabis and its chemical compounds. Cannabis sativa L. is one of the medicinal plant known for fibre, medicinal, psychoactive agents and oil. There are two names of Cannabis sativa one is Medical cannabis sativa (marijuana type), and another one is known Industrial Cannabis sativa (fiber type).. There is still a huge prejudice in society in relation to Medical cannabis sativa (marijuana type) due to its recreational use. In India, Cannabis sativa is also commonly known as Indian hemp, marijuana, Bhang, Ganja, and Charas, which are banned in India as an illicit drug. Sales and cultivation of Medical cannabis (marijuana type) are illegal in India. However, this scenario is changing, and the social resistance is decreasing for the medicinal use of Cannabis.

Keywords: Bhang, Cannabidiol (CBD), Charas, Cannabis sativa, Ganja, Illicit drug, Psychoactive compound, hemp, marijuana, Δ9-Tetrahydrocannabinol-THC.

INTRODUCTION

Cannabis grows profusely in the world and designates Cannabis sativa, Cannabis indica, and Cannabis ruderalis. The major cannabinoids responsible for its action include the psychoactive Δ-9 Tetrahydrocannabinol (THC), the nonpsychoactive Cannabidiol (CBD), and Cannabinol (CBN). Interestingly, THC and CBD have antagonistic effects on addiction-related behaviors. THC boosts drug use, whereas CBD has low hedonic property and impedes drug seeking. CBD is generally well tolerated with a good safety pro?file, yet reported adverse effects may be as a result of drug–drug interactions between CBD and patients' existing medications.[1]

Randomized clinical trials provide mixed support of marijuana for treatment of chronic pain and spasticity (Stockings et al., 2018; Whiting et al., 2015) and weak support for treatment of nausea and vomiting due to chemotherapy, weight gain in HIV infection, and sleep disorders (Whiting et al., 2015). Advocates, however, tend to view marijuana as useful for a wider range of medical conditions. Studies show that individuals who use medical marijuana are also likely to use it for recreational or non-medical purposes (Choi et al., 2017; Compton et al., 2017). While the likelihood of using medical marijuana increased among U.S adults between 2013–2015

(Han et al., 2018), pattern of use remained unchanged among adults who reported using marijuana exclusively for medical purposes over the same period. As policies continue to evolve regarding medical marijuana authorization practices and to help inform prevention efforts for substance use disorders, this study presents nationally representative data to characterize three groups of marijuana users: those who use it for 1) only non-medical purposes, 2) only medical purposes, and 3) medical and non-medical purposes.[2]

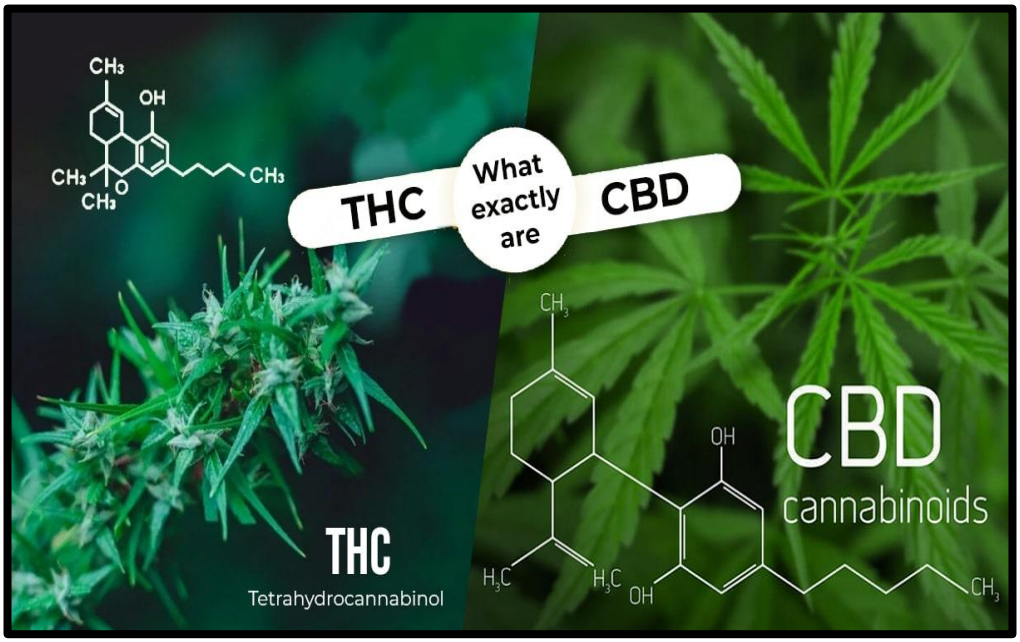

Figure: Chemical Constituents of Cannabis

HISTORY

The cannabis or hemp plant has been known since antiquity and grows in almost all parts of the world, but has been known principally as a source of useful fibre for the manufacture of textiles and rope. In most fibre-producing areas, the plant was not used as a drug. Geographic and climatic factors modify the content of pharmacologically active material in the plant, and only in some regions was this content high enough to lead to the discovery that the plant, and especially its resin, had important drug actions. Knowledge of these actions appears to have arisen first in the Himalayan region of central Asia and spread gradually from there to India, Asia Minor, North Africa, and across the desert to sub-Saharan Africa and the rest of the African continent.[3]

INDIAN HISTORY

In India, the plant was used both medically and nonmedically. Its social and religious uses were related most notably to the festival of Durga Puja. On a few other occasions during the year it was also used in family celebrations such as marriages and births to induce a relaxed and sociable mood and a good appetite. Only the weaker preparations were used: ëbhangí (comparable to marijuana) was taken by mouth, and the slightly stronger preparation ëganjaí was smoked, but the most potent preparation, ëcharasí (known elsewhere as hashish) was not used for these purposes. Indeed, use of charas was not socially approved for any purpose, and its devotees were regarded as ëbad charactersí or outcasts.[4]

Bhang, the drink made of cannabis leaves, milk, sugar, and spices, has been part of 'India's living since time immemorial. It originates in the legends of the Shiva, designated as the 'Lord of Bhang' who planted the cannabis fields in the district of Kullu in Himachal Pradesh. Not without reason that hemp use has touched almost every major spiritual tradition on earth at some point in Indian history. The worship of the hemp plant in India thus emanates from this sacred lore, though it is intriguing that the worship rituals are shrouded in secrecy. The worship of the hemp plant was practised among the Kols of Kuamon region, and the Kunbis of western India. According to The Vedas, cannabis was one of five sacred plants and a guardian angel lived in its leaves.[5]

Figure: The wild growth of Cannabis sativa in Himalayan region

Cannabis also formed part of the therapeutic armamentarium of traditional Indian medicine, and many of the uses were similar to those for which it is currently advocated in our own society. Among its claimed benefits were sedative, relaxant, anxiolytic and anticonvulsant actions all of which also made it useful in the treatment of alcohol and opiate withdrawal ñ analgesia, appetite stimulation, antipyretic and antibacterial effects, and relief of diarrhoea.[6]

UPDATE OF CANNABIS

Marijuana's use as an herbal remedy before the 20th century is well documented. However, modern medicine adheres to different standards from those used in the past. The question is not whether marijuana can be used as an herbal remedy but rather how well this remedy meets today's standards of efficacy and safety. We understand much more than previous generations about medical risks. Our society generally expects its licensed medications to be safe, reliable, and of proven efficacy; contaminants and inconsistent ingredients in our health treatments are not tolerated. That refers not only to prescription and over-the-counter drugs but also to vitamin supplements and herbal remedies purchased at the grocery store. For example, the essential amino acid ltryptophan was widely sold in health food stores as a natural remedy for insomnia until early 1990 when it became linked to an epidemic of a new and potentially fatal illness (eosinophilia-myalgia syndrome). When it was removed from the market shortly thereafter, there was little protest, despite the fact that it was safe for the vast majority of the population. The 1,536 cases and 27 deaths were later traced to contaminants in a batch produced by a single Japanese manufacturer[7]. The boundaries drawn in this summary between cannabis and isolated cannabinoids is based on the following considerations:

a. To avoid confusing terminology;
b. The composition, bioavailability, pharmacokinetics and pharmacodynamics of botanical cannabis differs from extracts or purified individual cannabinoids;
c. The bioavailability of active cannabinoids in cannabis, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), cannot be predicted because differences in smoking or vapor inhalation vary between users and types of delivery systems. In contrast, a fixed oral dose of a cannabinoid can be quantified in plasma or whole blood samples, yielding relatively predictable results;
d. To avoid extrapolating to cannabis conclusions drawn from meta-analyses and primary sources reporting efficacy of purified and medically approved cannabinoid formulations at fixed doses, from randomized controlled trials (RCT). Approved cannabinoids are oral or sublingual spray preparations, whereas cannabis is used predominantly by smoking, inhalation from water pipes or vaporizing, a rapid form of brain delivery considered a route of administration with higher addiction potential for some drugs, although this principle is not established for cannabis5, 6, 7,8 (see Pharmacokinetics, below);
e. To avoid extrapolation and appropriation of safety data generated from isolated and medically approved

cannabinoids (with known doses) to whole plant cannabis, for which there are no guidelines for doses[8]

CANNABIS SATIVA: ETHNOBOTANY

Cannabis contains hundreds of specialized metabolites with potential bioactivity, including cannabinoids, terpenes, and flavonoids, which are produced and accumulated in the glandular trichomes that are highly abundant mainly on female inflorescences. Bioplastics, Biofuels, and Biopesticides are some of the innovative applications of the plant. These compounds and derivates thereof are involved in the treatment of disease conditions such as cancer, Alzheimer's, multiple sclerosis, chronic pain and inflammation, glaucoma, and many others. A recent study revealed that cannabinoids block cellular entry of multiple SARS-CoV-2 variants and exhibited a potential to prevent as well as treat SARS-CoV-2 infection. Cannabis species have long been used as folk traditional medicine in different regions of India and the compounds from Cannabis are used against, reactive oxygen species (ROS), cancer and microbial infections including both bacterial and fungal strains. The global cannabis market value has been estimated at $214–344 billion USD and legal markets are projected to expand in the next few years. Legalization or decriminalization of cannabis (Cannabis sativa L.) has been rapidly increasing worldwide over the past two decades. Further, over 70 countries have legalized some form of medical use of cannabis, while few countries including Canada, Uruguay, Mexico, The Netherlands, Spain, South Africa, and parts of the United States (24 US States) have legalized cannabis for adult use.[9]

Cannabis sativa has been used by innumerable ethnic societies in Asia. Uttaranchal (India) is an ethnic region where the plant is a part of the local culture. Industrial Cannabis sativa (fiber type) has been employed medicinally in Ireland since at least the Anglo-Saxon era, more than 1000 years ago. Its use came to the fore, however when William B. O'Shaughnessy, an Irish physician in India, became familiar with the versatility of Indian hemp in the treatment of rheumatic diseases, tetanus, cholera and epilepsy in 1838. Majority of historians believe that the Hemp plant is indigenous to both Central Asia and the Indian subcontinent and is widely found in the Himalayan Mountain regions (Figure-1) extending to India, Pakistan, China, Afghanistan, Nepal and even Bhutan and Myanmar. Scriptures like Vedas have estimated the plant to be at least 3400 years old and is even considered a sacred Indian plant.[10]

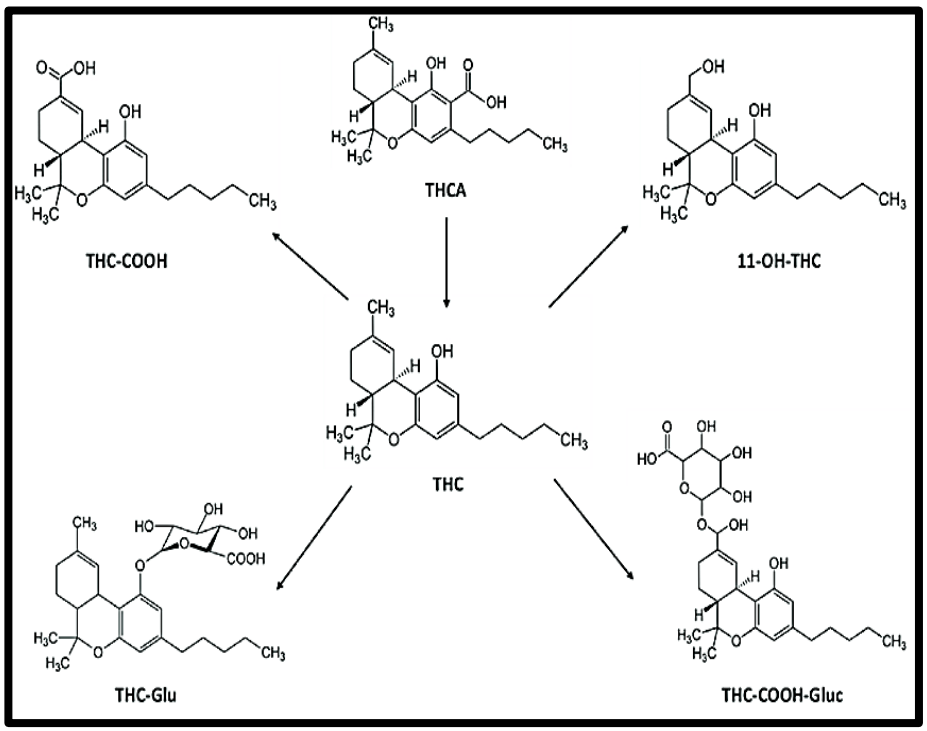

Figure: Chemical structures of Δ9-tetrahydrocannabinol (THC), its acidic precursor, and its metabolites.

PHYTOCHEMISTRY

The plant Cannabis sativa has been widely used by humans over many centuries as a source of fibre, for medicinal purposes, for religious ceremonies and as a recreational drug. Cannabis sativa L. (C. sativa) is an annual dioecious plant, which shares its origins with the inception of the first agricultural human societies in Asia. The abundant phytocannabinoids produced by Cannabis, has been used as medicine for centuries. On the other hand, its narcotic effects caused the plant to be subjected to many decades of worldwide strict regulations.[11]

Over the course of time different parts of the plant have been utilized for therapeutic and recreational purposes, for instance, extraction of healing oils from seed, or the use of inflorescences for their psychoactive effects. The key psychoactive constituent in Cannabis sativa is called Δ-9-tetrahydrocannabinol (Δ-9-THC). Amongst these compounds are the terpenes (volatile organic compounds also found in the essential oils of many plants) and the cannabinoids (or phytocannabinoids) that have pharmaceutical effects in humans. Cannabis terpenes and cannabinoids are manufactured in the secretory cavity of specialized structures on the surface of the plant, called glandular trichomes.

These crystal-like outgrowths are densely concentrated on female flowers and in other aerial parts of Cannabis. Δ9- tetrahydrocannabinol (THC) was the first cannabinoid to be isolated from Cannabis and is highly concentrated (in its carboxylated form) in modern Cannabis drug chemotypes. In addition to its well?known psychoactive effects, Δ9-tetrahydrocannabinol (THC) potentially exerts a variety of therapeutic activities including analgesic (pain-relieving), anti-inflammatory, and possibly anticancer properties. Cannabinoids are isolated from leaves, flowers, stems, roots and seeds, but the main source of phytocannabinoids are trichomes of unfertilized female flowers, which secrete a resin loaded of phytocannabinoids, as the THC.[12]

MEDICINAL USE OF CANNABIS

1. HISTORICAL BACKGROUND

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2. PHARMACOKINETICS

Cannabinoids can be administered by a variety of routes. Because of their high lipid solubility, topical administration is possible in such locations as the eye or the nasal mucosa. However, this has been of very limited applicability, because preparations of THC available in the past tended to be irritating to the eye. However, newer vehicles that permit lipid-soluble materials to be applied to the eye in aqueous solution may make this route of greater interest again. In theory, percutaneous absorption, as from a drug-impregnated skin patch, should be possible, but the absorption would be very slow and not clinically useful. Oral administration results in a slow and variable absorption, with a bioavailability of 10% to 20%, and usually less than 15%. There is also a high hepatic uptake from the portal venous blood, and an active first-pass metabolism in the liver. Nevertheless, this does not result in a loss of pharmacological activity, because the major firstpass metabolite, 11-hydroxy-THC, is at least as potent a psychoactive agent as THC itself. THC can also be converted to a hemisuccinate and administered as a rectal suppository. Absorption is quite good by this route, with much higher bioavailability than

after oral administration. In addition, rectal absorption delivers the drug directly into the systemic circulation, thus avoiding the first-pass metabolism.[15]

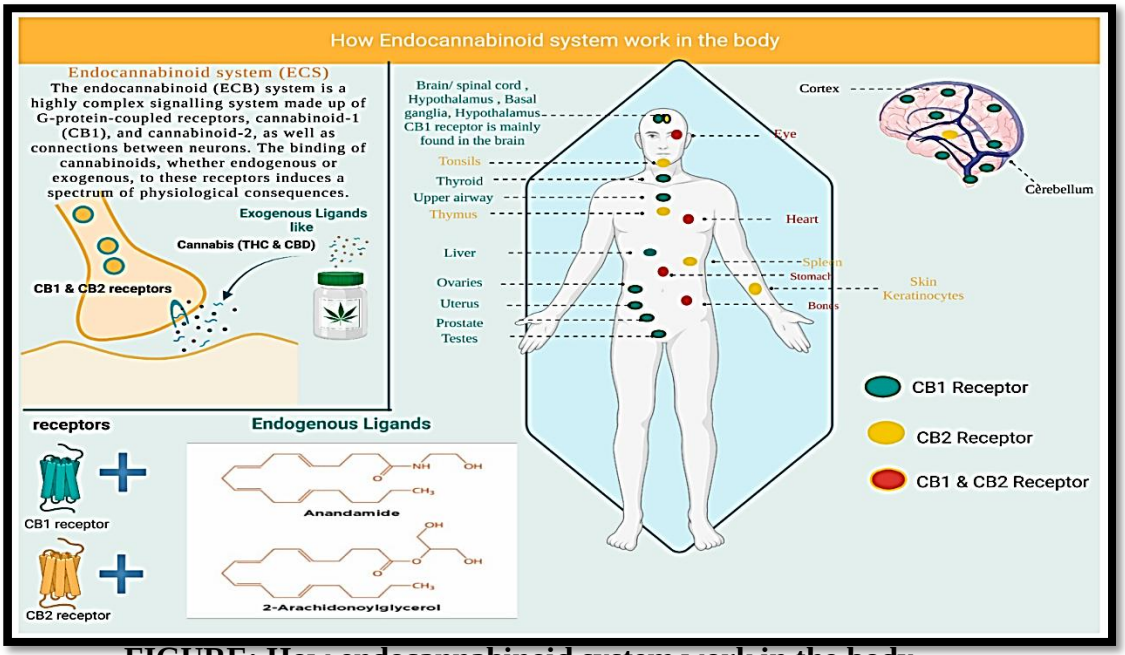

FIGURE: How endocannabinoid system work in the body

Intravenous injection or infusion is possible, but because of the very low water solubility of cannabinoids, a special formulation must be used, such as a complex of the cannabinoid with plasma protein, or a solution in a water-miscible organic solvent. Without such formulations, almost no active material can be delivered, and intravenous toxicity is due essentially to injection of insoluble particulate material. Intravenous administration of suitable preparations gives a very rapid onset of action, but because of dosage limitations to avoid excessive intensity of the peak effect, the duration of action is short[16]

PHARMACOLOGICAL EFFECTS

1. ACUTE EFFECTS

Both crude cannabis and pure THC have a wide range of pharmacological effects, only some of which are of poten?tial therapeutic interest.

1. Central nervous system: Cannabis acts essentially as a central nervous system (CNS) depressant; therefore, its main acute effects in many ways resemble those of alcohol. It produces drowsiness and decreased alertness, being synergistic with alcohol, barbiturates and other CNS depressants in this respect. Similarly, although THC has minimal respiratory depressant effect by itself, it may be synergistic with other depressants. Cognitive effects include impairment of short term memory, slowed reactions, decreased accuracy of psychomotor task performance and decreased selectivity of attention (greater interference by extraneous stimuli). Motor coordination and muscle tone are also decreased, resulting in ataxia. As a result of all of these effects, it causes poorer performance in simulated driving or flying tasks. However, the risk for real life driving may be less than with equivalent levels of alcohol intoxication because the cannabis users appear to be more cautious and less aggressive.[17]

Low doses of cannabis typically induce mild euphoria, relaxation, increased sociability and decreased anxiety. However, high doses often result in dysphoria, increased anxiety and panic reactions, especially in inexperienced users. Similarly, low doses tend to increase sensory acuity, often in a pleasurable way, whereas high doses may cause sensory distortion, hallucinations and even an acute toxic psychosis that is usually of short duration after the drug is discontinued.[18]

Pain perception is diminished, and pain tolerance increased, by a central action of THC that is separate from that of opioid analgesics. It is exerted at CB1 receptors in the central grey matter, and local injection of THC or its synthetic analogues at this site is effective in alleviating pain. However, there also appear to be spinal cord sites and peripheral sites that contribute to the analgesic action. The CB1 receptor blocker SR 141716A prevents the

analgesic effect of THC but not of morphine, whereas naloxone blocks the morphine analgesia but not the analge?sia produced by THC or its analogues.[19]

2. Neuromuscular system: Apart from the centrally mediated effect on skeletal muscle tone, there appears to be a more peripherally mediated antispasticity action. It is not clear whether this is exerted in the spinal cord or at peripheral sites such as the nerve-muscle junction.

3. Cardiovascular effects: One of the most consistent and reliable signs of acute action of cannabis is tachycardia, with increased cardiac output and correspondingly increased myocardial oxygen requirement. These effects are generally mild and of no pathological significance, but the increased myocardial workload could in theory become dangerous in an individual with some degree of coronary insufficiency. The tachycardia may possibly be a compensatory reaction to cannabis-induced vasodilation, which is often revealed as orthostatic hypotension.[20]

4. Respiratory system: One of the manifestations of smooth muscle relaxation by cannabis or THC is bronchodilation, with resulting decrease in airway resistance. This is an acute effect, but with chronic use it tends to be offset by bronchial irritation caused by the particulate fraction of cannabis smoke. Because cannabis smoke is similar in most respects (other than cannabinoid content) to tobacco smoke, the consequences of chronic exposure to cannabis smoke are similar to those of tobacco smoke. Eye: Cannabis and THC have been shown repeatedly to lower the intraocular pressure (IOP) by a mechanism that is not yet understood. This effect can be produced by systemic administration at doses that also produce the characteristic CNS effects, and rather inconsistently by local application to the eye.[21]

5. Immune system: In vitro exposure to very high concentra?tions of THC results in decreased function of macrophages, lymphocytes and natural killer cells. In vivo, however, the observations are highly variable in different studies, and it is not yet clear whether smoking cannabis significantly Kalant 84 Pain Res Manage Vol 6 No 2 Summer 2001 kalant.qxd 8/1/01 10:25 AM Page 84 affects immune functions. Experimental studies in mice have suggested that resistance to legionella infection may be decreased by THC. The risk of pulmonary aspergillosis is increased in patients with acquired immune deficiency syndrome (AIDS), but it is difficult to know whether cannabis acts as an immunosuppressant or simply as the source of the fungal contaminant. In any case, the in vitro effects on immune cells are probably not produced via CB1 receptors because they are also produced by cannabinoids that lack the psych activity of THC.[22]

6. Chronic Effects

In contrast to the potential therapeutic interest in the acute effects described above, changes in these effects that may occur with chronic use are linked mainly to the production of adverse effects that may limit the therapeutic usefulness of cannabinoids.[23]

7. CNS: Prolonged daily use of cannabis has been linked to a variety of cognitive changes, including poor memory, vagueness of thought, decreased verbal fluency and learning deficits that are not always fully reversible when use of the drug is stopped. High-dose, daily use can give rise to a chronic intoxication syndrome, characterized by apathy, confusion, depression and paranoia. Cannabis dependence that meets the Diagnostic and Statistical Manual of Mental Disorders, 3rd edn, revised (DSM-III-R) criteria has been well documented in regular heavy users. Among the components of this dependence are increased tolerance to most of the effects of cannabis, and physical dependence in the form of a relatively mild spontaneous withdrawal syndrome or a more severe one precipitated by the CB1 antagonist SR 141716A. This precipi?tated withdrawal is analogous to the reaction provoked by naloxone in a dependent opiate user. Cannabis use has also been reported to precipitate clinical relapse in compensated schizophrenics, producing a picture that differs from that of spontaneous relapse in which cannabis use may be merely a symptom. Finally, the offspring of women who smoke cannabis during pregnancy have been reported to show subtle but apparently permanent cognitive and person?ality changes (impulsiveness, poor memory, decreased ver?bal fluency and verbal learning) when they reach school age.[24]

8. Respiratory system: Two relatively large scale studies of pulmonary function in chronic cannabis and tobacco smokers have given contradictory findings with respect to chronic obstructive pulmonary disease (COPD). One study, using a ëconvenience sampleí (ie, recruited through advertisements) of young chronic smokers of tobacco, marijuana or both, as well as nonsmokers, found a clear linkage of COPD to tobacco smoking, but not to marijuana

smoking. In contrast, a larger study using a systematic population sample subjected to very similar pulmonary function tests found a significant link between COPD and marijuana smoking, as well as an additive effect of tobacco and marijuana. The reason for the difference between the findings of the two studies is not yet entirely clear, but the two agreed that chronic inflammatory changes were definitely increased in cannabis smokers.

Chronic inflammatory chest disease has been reported to be present in over 60% of long term daily smokers of cannabis, in some studies. Precancerous changes in bronchial epithelial cells have been described in such users, and there are a number of case reports of upper airways malignancy or premalignant changes in young smokers of cannabis (aged less than 30 years, ie, much younger than is typical of tobacco-induced bronchial carcinoma). Although one prospective study of a large clinic population found no apparent increase in risk of lung cancer in cannabis users compared with that of nonusers, this study is flawed by its inclusion, in the group of cannabis users, of individuals who had used it as little as six times in their life. A much better designed recent casecontrol study of patients with proven upper airways cancer indicated a significant increase in risk among cannabis smokers, even after correction for concurrent tobacco use, and the increase in risk was proportional to the frequency and duration of cannabis use. The authors of the latter study systematically considered possible sources of error, such as selection bias, misclassification of cannabis exposure, low power and precision, etc, but were able to discard these by appropriate statistical comparisons of the control group with the general population. They recognized the need for larger scale comparisons as more long term cannabis smokers become available for study, but their findings point to a significant risk. This is consistent with the experimental demonstration of mutagenicity of cannabis smoke in the Ames test, which is probably not an effect of THC but of the particulate fraction of the smoke.[25]

Other systems: Heavy smokers of cannabis have shown various endocrine changes, including decreased testosterone levels and reduced sperm counts in males, and decreased luteinizing hormone and prolactin levels in the luteal phase of the menstrual cycle in females, resulting in shorter periods and more anovulatory cycles. However, the clinical importance of these changes is uncertain, because tolerance to these effects of cannabis may develop. Decreased levels of thyroxine and corticosteroids have been found in experimental animals receiving high doses of cannabinoids, but such changes have not been clearly demonstrated in humans. Similarly, high doses of THC have been found to impair protein and nucleic acid synthesis in rats, but the significance of these findings for humans remains unclear. Tolerance also develops to the acute cardiovascular effects of cannabis, and chronic use has not been shown to cause any significant harm to the cardiovascular system.[26]

INTERNATIONAL PERSPECTIVE ON MEDICAL USE OF MARIJUANA

A number of major reviews of the possible therapeutic uses of cannabis and cannabinoids have been carried out in several countries in the past seven years. A report of the Royal Pharmaceutical Society of Great Britain dealt with actual protocols for proposed multicentre clinical trials of smoked marijuana versus oral THC for the treatment of postoperative pain and of muscle spasm in multiple sclerosis. The other reports, however, presented more general coverage of the nature of cannabis and cannabinoids, their potential therapeutic uses and their limitations. It is, therefore, informative to review their conclusions briefly, to see what measure of agreement or disagreement there is among them.

The report of the National Drug Strategy of Australia concluded that there is good evidence of the effectiveness of THC as an antiemetic, reasonable evidence for the potential therapeutic use in glaucoma, and suggestive evidence for possible use as an analgesic, an antiasthmatic agent, an anticonvulsant and an antispasticity agent in multiple sclerosis. It called for properly controlled trials dealing with these potential indications, as well as with the wasting syndrome and depression in patients with human immunodeficiency virus/AIDS. However, all of these recommendations dealt with pure synthetic cannabinoids, and not with clinical trials of smoked marijuana[27]

The British Medical Association Report recommended further clinical research to establish suitable methods and routes of administration and optimal dosage for therapeutic use in nausea and vomiting (including well controlled comparisons with ondansetron and other 5-hydroxytryptamine3 antagonists); chronic refractory spastic disorders; chronic, terminal and postoperative pain; poorly controlled epilepsy; strokes and CNS degenerative disorders; and glaucoma. It also recommended further study of cannabinoid effects on the immune system, not with respect to possible use as an immunosuppressant, but rather to see whether cannabinoids are safe to use in patients with

already compromised immune systems. It specifically rejected the idea of therapeutic use of smoked marijuana or of unstandardized herbal preparations of cannabis, and points out the potential problems of cannabis tolerance and dependence in patients requiring long term therapy.

The report of a Select Committee of the British House of Lords recommended clinical trials of cannabis treatment in multiple sclerosis and chronic pain as a matter of urgency, but urged further research on alternative methods of administration, such as sublingual, rectal or aerosol-type inhalation, for rapid absorption without the adverse effects of smoking. It also pointed out the risks of acute intoxication, dependence and chronic health problems caused by cannabis itself and suggested that clinical trials of smoked marijuana should be considered only under special circumstances (of unspecified type). It suggested that one of the objectives of clinical trials should be to compare crude cannabis with pure THC, using doses that provide the same amount of THC by the same route, to see whether other constituents of cannabis add anything to the therapeutic effect.[28]

The report of the United States Institute of Medicine found good evidence for a useful analgesic action, complementary to that of opioids. It also found good evidence for a moderate antinauseant and antiemetic effect, again useful mainly as a supplement to conventional treatment. The appetite stimulation effect was considered promising, again mainly as a supplement to megestrol acetate. It recommended clinical trials of possible relief of muscle spasticity, but considered that oral THC might be superior to inhalation because of the longer duration of action. It did not consider movement disorders, epilepsy or glaucoma to be promising areas for clinical studies with cannabis. Finally, it recommended further research on the development of safe, reliable alternative delivery systems that could provide rapid onset of action; trials of smoked marijuana should be limited to short term use, and only for those indications for which present evidence suggests a probable beneficial effect.[29]

The conclusions set out in these reports have some important similarities and differences. All of them consider smoking to be an undesirable method of administering cannabis for therapeutic purposes, and recommend research on alternative methods of administration for rapid onset without the risks associated with smoking. All of them accept the antinauseant, antiemetic, appetite-stimulating, analgesic and antispasticity effects as worthy of further clinical trials. All of them recommend precise comparison of cannabis with pure THC or other cannabinoids. They disagree about the justification for clinical trials of cannabinoids for the treatment of asthma, epilepsy and glaucoma. Most of them accept the validity of clinical trials of smoked marijuana under special circumstances, primarily in terminally ill patients or for a limited time only in others. However, the Australian report refers only to pure cannabinoids, and a report of the Netherlands Health Council rejected completely the idea of any clinical use of crude cannabis, a view shared in a recent nongovernmental review in the United Kingdom.[30]

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