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MARIJUANA: MODERN MEDICAL CHIMAERA

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ABSTRACT

Marijuana has been used medically since antiquity. In recent years there has been a resurgence of interest in medical applications of various cannabis preparations. These drugs have been cited in the medical literature as potential secondary treatment agents for severe pain, muscle spasticity, anorexia, nausea, sleep disturbances, and numerous other uses. This article reviews the research literature related to medical applications of various forms of cannabis. Benefits related to medical use of cannabinoids are examined and a number of potential risks associated with cannabis use, both medical and recreational, are considered. There is a clearly identified need for further research to isolate significant benefits from the medical application of cannabinoids and to establish dosage levels, appropriate delivery mechanisms and formulations, and to determine what role, if any, cannabinoids might play in legitimate medical applications. It is also imperative to determine if reported dangers pose a significant health risks to users.

In Greek mythology, the Chimaera was a fearful creature with a lion's head, a goat's body, and a serpent's tail capable of vomiting flames like a dragon. Marijuana, a plant whose use traces to antiquity, seems to possess chimerical properties: imaginary, fanciful, or fantastic, as a purported therapeutic agent. This brief review will examine some of the claims made about this contemporary medical chimaera.

Globally, marijuana is the second most commonly smoked substance following tobacco (*World Drug Report,* 2006). It is also the most commonly used

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illegal drug in the United States and is accepted by many young adults as an illicit substance with a high degree of safety (Hashibe, Tashkin, Morgenstern, Greenland, & Zhang, 2005). Fifteen states, along with the District of Columbia, have approved some version of a medical marijuana law (Cohen, 2010).

There is evidence that within a strictly regulated medical environment, the risk-benefit profile for medical marijuana use is favorable (Cohen, 2010), but there are still unresolved concerns regarding the risks related to medical and recreational marijuana use. In a systematic review of the literature on cannabis use for chronic pain, Martin-Sanchez et al. (2009, p. 1354) concluded "no solid, conclusive data have emerged that would justify the use of cannabis as an alternative to the currently marketed and accepted therapeutic analgesic arsenal." Such observations are frequent in the medical literature and are often accompanied by calls for the rescheduling of marijuana in the United States from Schedule I to Schedule II, which would greatly facilitate the ability of researchers to obtain funding and conduct legitimate research on the medical effects of marijuana and its various derivatives, thus providing a foundation from which to make decisions based upon solid scientific evidence. The focus of this narrative will be on an examination of the risks and benefits associated with the use of marijuana and its derivatives based on the currently deficient research literature.

DRUG DELIVERY

Medical marijuana is available in some states within the United States either in herbal form utilizing dried parts of the *Cannabis* plant or via prescriptions (in all states) for Marinol (dronabinol), which is a synthetic version of delta-9 tetrahydrocannabinol (THC) in a sesame oil capsule or as a newer version of synthetic THC, Cesamet (nabilone), which reportedly possesses an improved absorption profile (Wang, Collet, Shapiro, & Ware, 2008).

A combination of THC (27mg/ml) and cannabidiol (25mg/ml), which are the two most prominently studied of the approximate 400 psychoactive cannabinoids found in the *Cannabis* plant, is available outside of the United States under the name Sativex. This liquefied version of marijuana extract is sprayed into the oral cavity and absorbed through mucosal tissue (Selvarajah, Emery, Gandhi, & Tesfaye, 2010; Wang et al., 2008).

BENEFITS OF MEDICAL CANNABIS USE

There are a wide variety of suggested medical uses for marijuana and its derivatives. Most have not been studied thoroughly, but some of the major suggested benefits are related to treatment for pain, nausea, anorexia, muscle spasticity, sleep, and as a synergistic agent to decrease the levels of opiates prescribed for pain.

In the first ever clinical trial of Sativex for intractable pain, Salvarajah et al. (2010) reported that this cannabis extract was no more efficacious than placebo in the treatment of 38 patients suffering with painful diabetic neuropathy. These researchers noted that depression and concomitant use of other pain medications were significant confounders in their study. Due to the particularly large placebo effect noted in this study, there appears to be a need for further research on the efficacy of Sativex for pain.

In a meta-analysis of double-blind randomized controlled trials of medical marijuana, Martin-Sanchez et al. (2009) reviewed 93 studies published prior to February 2008. Eighteen papers which met evaluation criteria for their study were included in the final analysis. Most of the studies employed a crossover design but did not allow for a sufficient washout period in order to clearly discount potential carryover effects of the medication. Also, there was a large number of sources of variability among the studies. None of the studies addressed potential for drug addiction nor did they account for possible recreational or other types of prior use of marijuana. The authors concluded that cannabis use in the treatment of pain presented more risks than benefits.

A comprehensive literature review of cannabis use in palliative care examined all the literature available since 1996 (Green & DeVries, 2010). The authors noted that considerable caution has been exercised by medical practitioners regarding the integration of cannabis-based medications into general palliative care, which includes attempts to make patients as comfortable as possible and improve their quality of life. After describing the analgesic benefits of cannabinoids with animal models, the authors noted that "systematic reviews on the efficacy of cannabis in pain control for humans suggests that there is as yet inconclusive evidence that cannabis has any major therapeutic role in pain management" (Green & DeVries, 2010, p. 2457). In commenting on cannabis use for multiple sclerosis (MS), the authors reported that there is little concrete evidence to support the use of cannabis to treat symptoms of MS such as ataxia, tremors, and spasticity, and note that adverse side effects are often reported. They also suggested that mood enhancing psychoactive effects may play a role in patient reports regarding their self-perceptions of the benefits of cannabis in treating tremors (Green & DeVries, 2010). On the positive side, the authors note that there has been a growing amount of literature suggestive of improvements in Quality of Life (QOL) outcomes such as improvements in sleep and abatement of depressive symptoms. They also noted reports in the literature on opioid-sparing effects which may have resulted from the improved analgesia derived from synergistic effects of opioid/cannabinoid preparations.

Peat reiterated the call for further study on the effects of cannabis in pain reduction and other symptoms of chronic illness (Peat, 2010). She cited numerous studies suggesting that both Cesamet (nabilone) and Sativex were potentially efficacious as adjunctive agents for the secondary treatment of chronic illness. She also noted that cannabinoids alone were unlikely to be helpful for the

treatment of MS but may offer "subjective improvement" from the patient's perception (p. 483). She cautioned that patients reporting benefits from smoked cannabis may see these improvements vanish if they resort to oral preparations. Peat concluded with the observation that cannabinoids should be considered as adjuvant therapies in the management of patients with complex pain and symptom control needs.

In a 10-week, double-blind, randomized, placebo-controlled trial of 135 patients with overactive bladder associated with MS, Kavia et al. (2010) attempted to determine the efficacy, tolerability, and safety of Sativex. They concluded that Sativex did provide some improvement in Quality of Life indicators related to bladder dysfunction, but the results did not reach statistical significance.

In another examination of the effectiveness of Sativex in the alleviation of spasticity in patients with MS, Wade, Collin, Stott, and Duncombe (2010) conducted a meta-analysis of three randomized, placebo-controlled, double-blind studies which included 666 people with MS related spasticity. The authors reported that large numbers of subjects experienced at least one adverse event. Some of these adverse events were of moderate severity, while those of a more serious nature were resolved, leading the authors to conclude that Sativex did reduce spasticity and was well tolerated by the subjects.

RISKS ASSOCIATED WITH MEDICAL CANNABIS USE

Adverse Medical Effects

In a systematic review of the literature related to adverse effects associated with medical cannabis use over the past 40 years, Wang et al. (2008) uncovered 164 serious adverse events among patients receiving cannabis therapy as compared to 60 such events in the controls. Serious adverse events included primarily respiratory and nervous system disorders. The authors concluded that "short-term use of existing medical cannabinoids appeared to increase the risk of nonserious adverse events" (p. 1669).

Marijuana Abstinence Syndrome

Even though drug experts may not be in agreement that marijuana should be classified as an addictive substance, there is significant evidence that a small percentage of users exhibit signs of dependence and that if they attempt to discontinue use, they experience a specific set of symptoms that have been labeled the "marijuana abstinence syndrome." Bodily function is altered by marijuana use and withdrawal symptoms affect more than 50% of regular users. Withdrawal symptoms include: anxiety, depression, decreased appetite, headaches, insomnia, irritability (sometimes accompanied by violence), muscle tension,

nausea, nightmares, and unpleasant vivid dreams. The severity of these symptoms has been associated with duration and frequency of use (Julien, 2005; Lamarine & Sbarbaro, 1998).

Lung Damage

Smoking marijuana has been found to produce an almost fivefold increase in blood carboxyhemoglobin, nearly a threefold increase of inhaled tar, and retention in the lungs of one-third more tar as compared with smoking tobacco. Also, researchers have noted that smoking dynamics differ between marijuana and tobacco smoking. For marijuana, depth of inhalation, volume of smoke inhaled, and a significantly longer duration of breath holding have been observed (Wu, Tashkin, Djahed, & Rose, 1988).

Bronchodilation has been associated with short-term exposure to marijuana, while respiratory symptoms indicative of obstructive lung disease have been related to longer exposure to smoked cannabis. (Hashibe et al., 2005; Tashkin, 2009; Tetrault, Crothers, Moore, Mehra, Concato, & Fiellin, 2007). The concurrent use of tobacco and marijuana may produce a synergistic effect accelerating respiratory problems and risk for chronic obstructive pulmonary disease (COPD) (Tan, Lo, & Jong, 2009).

Heart Disease

Any organic substance that is burned and inhaled will deliver a significant amount of carbon monoxide which interferes with hemoglobin's ability to transport oxygen within the body, increasing the risk for heart attack. Marijuana, which purportedly burns less efficiently than tobacco, is likely to produce even higher levels of carbon monoxide than tobacco (Green & DeVries, 2010; Macleod & Hickman, 2010). Several studies have noted risks for cardiovascular disease associated with the regular use of marijuana, particularly among aging users (Hall, 2009; Kaiser Permanente, 2002; Kocabay, Yildiz, Duran, & Ozkon, 2009; Tormey, 2001).

Cancer

Inhaled smoke from marijuana contains many of the same carcinogenic substances found in the tar from smoked tobacco. Increased risk for glioma, prostate, and cervical cancer have been noted among non-tobacco using marijuana smokers. Cancers of the head and neck have also been associated with marijuana use. Marijuana use by pregnant women has been linked to increased occurrences of childhood leukemia, astrocytoma, and rhabdomyosarcoma. More research is needed to adequately evaluate the risks for cancer associated with marijuana use, but the current assessment must be viewed as reason for concern (Hashibe et al., 2005; Kahan & Srivastava, 2007).

Anxiety

In a comprehensive review of the literature up to 2008 regarding the association of cannabis with anxiety-related problems, Crippa et al. (2009) identified a consistent relationship between frequent marijuana use and higher anxiety levels but not necessarily anxiety disorders. They also noted a higher prevalence of comorbidity between regular marijuana use and panic and social anxiety disorders. The authors suggested that anxiety was also related to the cannabis withdrawal syndrome. They concluded "while there is little doubt that cannabis use can cause anxiety symptoms, it is less clear that it can increase the risk of developing anxiety disorders which persist after the cessation of use" (p. 518).

Psychosis

A relationship between cannabis use and psychotic symptomology has been consistently noted. In a review of longitudinal research examining the relationship between marijuana use and the onset of psychotic symptoms, Degenhardt and Hall (2006) examined six studies, from five countries, targeting adolescents and young adults. They found that regular cannabis use was a predictor of increased likelihood of schizophrenia diagnosis or symptomology. The authors concluded that regular cannabis use is predictive of an increased risk for schizophrenia, a relationship that persists even after controlling for confounding variables. They cited biologically plausible mechanisms which may account for this observation and also noted epidemiological events that may be contributing to this trend: a significant increase in THC levels in cannabis over the last few decades as well as a sharp decline in the age of initiation of marijuana use leading to a longer duration of use.

Caspari (1999) noted that schizophrenic patients with prior marijuana abuse had a significantly greater number of re-hospitalizations, greater impairment in psychosocial function, and worsened psychopathological syndromes (i.e., "thought disturbances" and "hostility").

Other Mental Health Problems

A large number of studies have concluded that marijuana use is related to numerous psycho-social problems ranging from prolonged adolescence to possible psychosis (Caspari, 1999; Medina, Hanson, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2008; Realini, Rubino, & Parolaro, 2009). The work of Solowji et al. (2002) indicated that long-term, heavy marijuana use led to impairments in attention and memory that continued after the period of intoxication and became progressively more serious following increased years of marijuana use.

Among adolescent marijuana users, early initiation was associated with higher risk for dropping out of high school, delinquency, having multiple sex partners, inconsistent condom use, underestimating the harmfulness of drugs,

smoking tobacco, and manifesting a higher incidence of problems related to the consequences of combining alcohol with marijuana. Additionally, adolescent early initiators were more likely to associate with friends who exhibited deviant behaviors (Brook, Balka, & Whiteman, 1999).

Subtle deficits in memory, executive function, and attention have been noted in adult marijuana users. Adolescent marijuana users, even after a month of monitored abstinence, demonstrated subtle neuropsychological deficits when compared to nonusers (Medina et al., 2007). Medina et al.'s (2007) research conclusions have reinforced the earlier findings of Pope and Yurgelun-Todd (1996) that heavy marijuana use was related to residual neuropsychological effects even after 24 hours of supervised abstinence.

Summary of Health Risks

McGuiness (2009) summarized the literature succinctly with the observation that marijuana

> is not a benign substance. Inhalation of marijuana smoke is more harmful than tobacco smoke; cannabis smoke delivers 50% to 70% more carcinogens. Other physiological effects include decreased immune function, higher rates of cardiac arrhythmias, and documented cases of cerebellar infarction. Mood and cognitive effects of marijuana include exacerbation of depression and anxiety (including panic attacks), as well as memory problems, that may persist for a month after last use. Cannabis use is a risk factor for psychosis in genetically predisposed people and may lead to a worse outcome of schizophrenia. (p. 19)

In a systematic review of the literature, which included more than 5,000 papers, Reece found that in addition to many of the risks noted above by McGuiness, marijuana use is a risk factor for bipolar disorder, amotivational state, reduced lung density, lung cysts, chronic bronchitis, myocardial infarction, altered bone metabolism, and teratogenic effects on brain development of the fetus. Chronic marijuana use has been associated with teratogenic, oncogenic, and mutagenic effects related to dose and duration of use (Reece, 2009).

CONCLUSION

Currently the evidence concerning the benefit/risk outcomes related to the use of medical cannabis in its various formulations is still insufficient. One significant complication relates to the delivery mechanism for cannabinoids. Most reports concerning user preferences suggest that smoked cannabis is perceived as more effective and more desirable than oral and sublingual preparations. Clinical evidence supports this perspective since oral and even sublingual preparations are absorbed more slowly and less efficiently than smoked cannabis. Smoked cannabis presents other problems such as a significant health burden on

the respiratory system and difficulties prescribing measured dosages. Self-reports suggest that inhalation does allow for fairly specific titration of dosage from the subjective perspective of the user (Peat, 2010).

Few of the clinical trials discussed in this review presented clear evidence of a statistically significant efficacy for cannabinoid preparations for the primary treatment of any major illness. There is considerable anecdotal and some scientific evidence that cannabinoids could be useful secondary treatment agents that contribute to QOL assessments for patients with seriously debilitating and painful conditions. There is also data suggestive of a synergistic opioid-sparing effect when cannabinoids are combined with opiate medications.

Risks associated with the medical use of cannibinoids appear to be relatively minor. The most often noted risks appear to be short-term increases in anxiety and anxiety-related problems. Another more serious concern is data suggestive of a possible causal relationship between marijuana use and psychosis; however, it appears most likely that any real effects are related to the precipitation of psychotic events in persons having a predisposition toward psychosis. An additional consideration is that approximately 9% of cannabis users develop a significant dependency on the substance (Mathews, 2010).

Addressing these concerns in the order listed above, anxiety seems to occur in users predisposed to anxiety and it is likely that the anxiety effects are dose-related and of a short duration with no long-term changes after discontinuation of the medication (Crippa et al., 2009).

Possible increases in psychosis appear inconsistent with long-term epidemiological data on the increased use of marijuana in the general population and the lack of a concomitant significant increase in the percentage of diagnosed cases of psychoses (Macleod & Hickman, 2010).

As far as addiction to cannabis is concerned, it should be considered in light of the fact that in many cases cannabis is proposed as either an alternative to opiates or as a synergistic agent to be used with opiates, potentially decreasing the required dose of opiate narcotic. There should be little argument that possible addiction to marijuana pales in comparison to the significantly higher established risk for opiate addiction in those afflicted with chronic pain (Mathews, 2010).

It is still too early for a final verdict on the role of marijuana and its derivatives in the medical treatment of pain, spasticity, and a wide variety of other conditions. Current trends in the medical research on cannabinoids are suggestive of a slow, cautious adoption of these drugs into the legitimate mainstream medical community and most likely their role will be as secondary treatment agents administered in a form other than the inhalation of the smoked plant (Peat, 2010). The jury will be out until more double-blind, randomized, placebo controlled trials are conducted. In view of the current restrictions on research with marijuana and its derivatives in the United States, a major step in facilitating the research agenda would be if the federal government and the Drug Enforcement Administration (DEA) were to reschedule cannabis from Schedule I to Schedule II

which would greatly facilitate researchers' ability to obtain grants to conduct needed medical trials.

In closing, as noted by Peat (2010), caution should be exercised in light of possible adverse effects from cannabinoids, particularly in patients whose illnesses are less serious. At the present, the acute effects of medical cannabis preparations appear relatively insignificant and able to be controlled by careful regulation of dosage. As far as recreational use is concerned, there is still a need for more and better data on this modern medical chimaera.

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