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Evaluating the Medicinal Uses of Cannabis

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ABSTRACT

Cannabis is the most frequently used illicit psychoactive substance in the world. Though it was long considered to be a soft drug, studies have proven the harmful psychiatric and addictive effects associated with its use. A number of elements are responsible for the increased complications of cannabis use, including the increase in the potency of cannabis and an evolution in the ratio between the two primary components, Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol. Synthetic cannabinoid (SC) use has rapidly progressed over the last few years, primarily among frequent cannabis users, because SCs provide similar psychoactive effects to cannabis. Cannabis does have therapeutic properties for certain indications. The use of the cannabis plant (Cannabis sativa L.) for the palliative treatment of cancer patients has been legalized in multiple jurisdictions including Israel. Its use for medicinal, ritual or recreational purposes results from the actions of cannabinoids in the cannabis plant. These therapeutic applications pertain only to certain cannabinoids and their synthetic derivatives. These compounds also produce the unintended adverse consequences of cannabis.

Keywords: Cannabis, Tetrahydrocannabinol (THC), Synthetic cannabinoid, Cannabidiol (CBD), Cannabinoid.

INTRODUCTION

Cannabis refer to the plant *Cannabis sativa, Cannabis indica,* and of minor significance, *Cannabis ruderalis*. *Cannabis sativa* is one of the most ancient psychotropic drugs known to humanity. The *Cannabis sativa* and *Cannabis indica* are two common species used for consumption. Between the two species, *C. sativa* has comparatively higher delta-9-tetrahydrocannabinol (THC) concentration while *C. indica* has comparatively higher cannabidiol concentration. Cannabis use has been documented as far back as 2900 B.C. Its use was well documented as the prime medicine for more than 100 illnesses and diseases in the U.S. pharmacopoeia in the 1800s through early 1900s [1] [2] [3]. Cannabis (also known as marijuana) is a psychoactive plant that contains more than 500 components, of which 104 cannabinoids have presently been identified. Two of these have been the subject of scientific investigation into their pharmacological properties: Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD).

Cannabis potency is primarily evaluated according to a sample's THC concentration. This is the primary psychoactive cannabinoid in cannabis. The adverse effects after acute or regular cannabis use are in direct relation to THC concentrations in the product. Its use for medicinal, ritual or recreational purposes results from the actions of cannabinoids in the cannabis plant. These compounds also produce the unintended adverse consequences of cannabis. Evidence of the use of cannabis for medicinal and ceremonial purposes goes back 4000 years. In 1854, the plant appeared in the United States Dispensatory and was sold freely in pharmacies in Western countries. It also appeared in the British Pharmacopoeia as an extract and tincture for over 100 years. In 1942, cannabis was removed from the United States Pharmacopoeia, and, with that, its legal medicinal use was stopped. Only in 1971 did Britain and most of the European countries outlaw the use of cannabis

according to the UN Convention of Psychotropic substances [4] [5].

Over the last few years, many studies have shown that CBD levels may also have an important impact. CBD may have a protective effect against certain negative psychological effects from THC. It may also be capable of antagonizing at least some of the adverse effects related to THC.3

Controversy and Legality Surrounding Cannabis

Recreational use of cannabis, as well as the use of the name "marihuana," was introduced into American culture after the Mexican Revolution of 1910 (PBS, 1998). During the depression, some research linked the use of cannabis with violence, crime, and other socially deviant behaviors (PBS, 1998). By the 1930s, a fear of cannabis had crept in, and by 1931, 29 states had outlawed cannabis, which eliminated its availability as an over-the-counter drug (PBS, 1998). In 1937, Congress passed the Marihuana Tax Act, effectively criminalizing cannabis by the use of an exorbitant tax for certain authorized medical uses (Marihuana Tax Act of 1937).

The 1960s brought a changing cultural climate and more lenient attitudes toward cannabis. Now government reports found that cannabis did not induce violence (PBS, 1998). The case of *Leary v. United States* (1969) challenged the constitutionality of the Marihuana Tax Act of 1937, and the U.S. Supreme Court found that the Act was unconstitutional. Congress quickly responded by enacting the Comprehensive Drug Abuse Prevention and Control Act in 1970, which created the Controlled Substances Act (CSA), a classification system and prescriptive restrictions for various drugs and substances—Schedules I through V (Comprehensive Drug Abuse Prevention and Control Act, 1970). Substances with a high potential for abuse without any accepted medical use (i.e., heroin, LSD, ecstasy) are included in Schedule I—the most stringent prescriptive restriction, which includes prohibition on most research using those controlled substances except under rigorous government oversight. The list of Schedule I Controlled Substances also includes cannabis, thereby continuing the restriction of cannabis use by prohibiting healthcare practitioners from prescribing cannabis [6] [7].

Cannabis use remained restricted until the first legalization of medical marijuana was approved in California in 1996; however, the federal government opposed the approval and threatened to revoke the prescription-writing abilities of physicians who recommended or prescribed cannabis [8]. It wasn't until 2000 that a group of physicians challenged the government's policy and prevailed in court with a decision to allow physicians to recommend but not prescribe medical marijuana (Marijuana Policy Project, 2014).Since then, 33 U.S. states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands have passed comprehensive medical marijuana programs (MMPs).

Another 13 states allow the use of low THC/high CBD products for medical reasons in some situations or as a legal defense to its use (National Conference of State Legislatures [NCSL], 2019). All provinces/territories of Canada (Government of Canada, 2016) have passed legislation legalizing the use of cannabis for medical purposes. With this legalization comes an increasing number of patients who use medical marijuana along with a larger population who use cannabis obtained through other means to self-treat various symptoms. Evidence supporting cannabis use to manage medical conditions is limited by legal restrictions on using cannabis for research purposes; thus, nurses are left without evidence-based, clinical resources when caring for patients who use medical marijuana products [9].

Statutory authorization of cannabis use for certain conditions is influenced by the limited available research, but more so influenced by advocacy groups and anecdotal evidence. Regardless of existing evidence or lack thereof, individuals are using cannabis and nurses will care for these patients more frequently [10] [11] [12]. To address the lack of guidelines for

nurses when caring for individuals using cannabis, the National Council of State Boards of Nursing Board of Directors appointed members to the Medical Marijuana Nursing Guidelines Committee to develop guidelines and recommendations to guide nurses' care of patients using medical marijuana, and those guidelines were published in July 2018 (National Council of State Boards of Nursing, 2018).

Cannabis for Medical Use

Cannabis is a generic term used for drugs produced from plants belonging to the genus *Cannabis*. It is one of the most popular recreational drugs; worldwide, an estimated 178 million people aged 15 to 64 years used cannabis at least once in 2012. Cannabis was included as a controlled drug in the United Nations' Single Convention on Narcotic Drugs, held in 1961 but its use is illegal in most countries.

Medical cannabis refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms. Cannabis (marijuana) has long been used for medical and recreational purposes. Cannabinoids can be classified into three subtypes, endocannabinoids (naturally present in human body), phytocannabinoids (present in cannabis plant) and synthetic cannabinoids (produced chemically) [13] [14]. Presently, over 60 different types of pharmacologically active cannabinoids have been identified and isolated from the cannabis plant. These include the exogenous cannabinoids such as the psychoactive THC and non-psychoactive cannabidiol, as well as the endogenous cannabinoids such as anandamide, which affects most systems in the human body, especially the central nervous system.

The cannabinoid binds to two types of G protein-coupled receptors: CB1, which are most abundant in the brain, and CB2, which are expressed on cells in the immune system where inflammation is modulated. Hence, cannabinoids are involved in psychomotor coordination, memory, mood, and pain [16] [17]. Given the expression of these receptors in the human body, and the interactions between cannabinoids with neurotransmitters and neuromodulators, such as dopamine, glutamate, serotonin, gamma-aminobutyric acid (GABA), it has been thought that cannabis may potentially confer some degree of medical benefit. Common commercially available cannabinoids for medical use are dronabinol capsules and nabilone capsules.

Testing of other synthetic cannabinoid compounds such as Epidiolex (GW Pharmaceuticals, Cambridge, UK), Namisol (Echo Pharmaceuticals, Weesp, the Netherlands) and Cannador (Society for Clinical Research, Berlin, Germany) are currently underway [18]. These cannabinoid formulations of varying THC or cannabidiol concentration and/or ratio have been widely studied for a variety of illnesses, most notably somatic conditions like pain and spasticity. More recently, there has been a growing interest in the neuroprotective potential of cannabinoids for neurological conditions, and the antipsychotic properties of cannabidiol [19]. Preclinical evidences suggest that cannabinoids may attenuate neurodegeneration by reducing excitotoxicity and oxidative damage via CB1 and CB2 receptors and receptor-independent mechanisms.

Cannabinoids can be administered orally, sublingually, or topically; they can be smoked, inhaled, mixed with food, or made into tea. They can be taken in herbal form, extracted naturally from the plant, gained by isomerisation of cannabidiol, or manufactured synthetically. Prescribed cannabinoids include dronabinol capsules, nabilone capsules, and the oromucosal spray nabiximols.

Some countries have legalized medicinal-grade cannabis for chronically ill patients. Canada and the Netherlands have government-run programs in which specialized companies supply quality-controlled herbal cannabis [20]. In the United States, 23 states and Washington, DC as of May 2015, have introduced laws to permit the medical use of cannabis; other countries have similar laws.

Cannabis Based Products for Medicinal Use

Cannabis based products that were previously listed in Schedule 1 can now be prescribed by doctors on the General Medical Council Specialist Register in the UK, on a named patient basis. Currently, general practitioners in the UK cannot prescribe them. These products are not licensed for specific medical indications but are used off licence for medicinal purposes in many countries, and are certified for quality according to good manufacturing practice. Examples include herbal cannabis (floral material from the cannabis plant) [21]. The recommended route of administration is through a medical vapouriser device and smoking is currently prohibited under NHS guidance. Extracts from the cannabis plant (such as cannabis oils containing THC) are also available for oral administration.

Some cannabis based products were already available for medicinal use before rescheduling in 2018. Sativex, an oral spray derived from the cannabis plant containing THC and CBD in a 1:1 ratio, is licensed for the treatment of spasticity in multiple sclerosis in 29 countries, including the UK, Israel, Canada, Brazil, and Australia [22]. However, meta-analysis suggests its effectiveness may be limited and it is not recommended by the UK's National Institute for Health and Care Excellence (NICE) because of poor cost effectiveness. Epidiolex, an oral CBD solution derived from the cannabis plant, was licensed by the US Food and Drug Administration in June 2018 for the treatment of seizures in two rare and severe forms of childhood epilepsy Lennox-Gastaut syndrome and Dravet syndrome.

Synthetic Cannabinoids for Medicinal Use

Synthetic cannabinoids (SCs) emerged in the 1970s when researchers were first exploring the endocannabinoid system and attempting to develop new treatments for cancer pain. Around the year 2000, SC appeared on the illicit drug market, where their prevalence had long been underestimated. Since then, their place in the market has steadily increased. More than 560 synthetic psychoactive substances have been identified on the illicit market [23]. There has been a steep rise in recent years with the appearance of 380 new synthetic drugs. Since 2008, more than 160 SCs have been identified in various products, 24 of which appeared in 2015.

Most SCs are manufactured by chemical companies located in Asia (China, South Korea). Today, intra-European production is closely monitored. Current legislation is frequently defeated and outwitted by manufacturers who regularly modify their chemical formulations, resulting in rapid turnover of SCs. Indeed, each SC is replaced by newer analogs within a year or two.

Dronabinol and nabilone are synthetically produced medicinal products that mimic the effects of THC. Dronabinol has an identical structure to THC, while nabilone has a related structure and is more potent than dronabinol, requiring lower doses to achieve clinical efficacy. Countries including the US, the Netherlands, Germany, Austria, and Croatia have licensed the use of both products [24]. They are licensed for the treatment of weight loss in patients with AIDS and of nausea and vomiting in people receiving chemotherapy who have failed to respond adequately to conventional anti-emetics. Nabilone is licensed in the UK while dronabinol is not licensed but can be prescribed on a named patient basis.

Medicinal Applications of Cannabis and Cannabinoids

Tetrahydrocannabinol (THC) is the psychoactive principle of cannabis, inducing the cannabis inebriation sought by many users. It's addictive potential and negative consequences are now well known. The effects of cannabidiol (CBD) are distinct and, in many cases, the opposite of THC's effects. CBD seems not to induce euphoria and seems to have antipsychotic, anxiolytic, antiepileptic, and anti-inflammatory properties.

According to an evaluation in 1999 by the Institute of Medicine in the United States on cannabis as a medication, the future of medical cannabis resides in isolating its cannabinoid components and their

synthetic derivatives. The variable composition within the raw cannabis plant and especially the differing THC/CBD ratios make therapeutic applications of these products quite complex. Various forms of cannabis have been studied to ascertain the therapeutic properties of cannabis [25].

In recent years, three molecules have been approved by the US Food and Drug Administration (FDA); a single molecule in Canada and Europe. Dronabinol, a synthetic THC, has been approved by the FDA in the treatment of anorexia in patients suffering from AIDS and as a second-line treatment in nausea and vomiting induced by cancer chemotherapies. Nabiximols, a combination of synthetic THC and CBD in equal proportions, is delivered in spray form. It has been approved in several countries (Canada, Europe), but not in the United States, as an adjunctive therapy in the treatment of spastic pain in patients with neurological disorders.

The most frequently studied cannabinoid forms were medications produced by pharmaceutical companies: nabilone, nabiximols, and dronabinol. The other evaluated cannabinoids included THC, CBD, and a combination THC/CBD. Evidences revealed moderate quality proofs in favor of nabiximols, nabilone, dronabinol, or THC/CBD in treating spasticity from multiple sclerosis. The same level of proof was shown for nabiximols or smoked THC in the treatment of chronic cancer pain and neuropathic pain. Proofs of lesser quality were found in favor of dronabinol or nabiximols in treating nausea and vomiting induced by chemotherapy and in weight gain in HIV/AIDS patients; for nabilone and nabiximols in treating sleep disorders; and for THC capsules in treating Tourette syndrome.

Cannabinoids seem to have some therapeutic interest in the following indications: epilepsy, addictions, psychotic disorders, anxiety, and sleep disorders. However, there are currently insufficient levels of proof. Indeed, a Cochrane review from 2014, for example, concluded that there were insufficient levels of proof for cannabinoids in the treatment of epilepsy. Nevertheless, cannabis-based treatments continue to elicit great interest. They remain the subject of preclinical and human research. In animal studies, CBD has shown significant antiepileptic activity, reducing seizure severity.

Recent studies in young patients suffering from severe, treatment-resistant epilepsy have shown that CBD may have a specific indication in these forms. Due to its implications in the reward system, endocannabinoid signaling represents a potential therapeutic target in treating addictions. The results from randomized, controlled trials suggest that CB1 receptor agonists such as dronabinol and nabiximols may be effective in treating cannabis withdrawal. Dronabinol may also decrease opioid withdrawal symptoms. Rimonabant, an inverse agonist of CB1 receptors, has shown promising effects in tobacco cessation; it also causes adverse psychiatric effects. Few clinical trials have examined the effect of cannabinoids in treating alcohol-use disorder; those examining rimonabant have shown negative results.

A potential advantage for CBD is its milder side effects: fewer extrapyramidal symptoms, less weight gain, and no hyperprolactinemia. Contrary to the effects of THC, several preclinical studies have shown that CBD may have anxiolytic effects. The understanding of the relationship between sleep and cannabinoids has been obscured by significant methodological differences resulting in mitigated results. The results from the literature seem to favor a beneficial effect of acute cannabis intoxication on sleep. On the other hand, regular cannabis use seems to have a negative impact on sleep quality. Different cannabinoids seem to have a differential impact on sleep. One study has suggested a therapeutic potential for dronabinol and nabilone on sleep disorders and nightmares. Studies specifically examining CBD have shown that when used at small doses, it may have some stimulant effects. At medium-to-high doses, it seems to have a more

sedative effect and thus may improve sleep quality. When CBD is associated with THC, it seems to reduce slow-wave sleep. Thus, there is preclinical evidence and some clinical evidence for therapeutic properties regarding a number of diseases. However, larger controlled clinical trials are needed to show efficacy and safety for each disorder.

CONCLUSION

Cannabis use and its negative consequences have increased over the last several years in parallel with increasing cannabis potencies. Improved knowledge of the endocannabinoid system and of exocannabinoids has proven that cannabis may have significant therapeutic effects. Future research should further explore the benefit-risk profile of medical cannabis use.

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