SPECIAL SECTION

A Brief Background on Cannabis: From Plant to Medical Indications

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Cannabis has been used as a medicinal plant for thousands of years. As a result of centuries of breeding and selection, there are now over 700 varieties of cannabis that contain hundreds of compounds, including cannabinoids and terpenes. Cannabinoids are fatty compounds that are the main biological active constituents of cannabis. Terpenes are volatile compounds that occur in many plants and have distinct odors. Cannabinoids exert their effect on the body by binding to receptors, specifically cannabinoid receptors types 1 and 2. These receptors, together with endogenous cannabinoids and the systems for synthesis, transport, and degradation, are called the Endocannabinoid System. The two most prevalent and commonly known cannabinoids in the cannabis plant are delta-9-tetrahydrocannabinol (THC) and cannabidiol. The speed, strength, and type of effects of cannabis vary based on the route of administration. THC is rapidly distributed through the body to fatty tissues like the brain and is metabolized by the cytochrome P450 system to 11-hydroxy-THC, which is also psychoactive. Cannabis and cannabinoids have been indicated for several medical conditions. There is evidence of efficacy in the symptomatic treatment of nausea and vomiting, pain, insomnia, post-traumatic stress disorder, anxiety, loss of appetite, Tourette's syndrome, and epilepsy. Cannabis has also been associated with treatment for glaucoma, Huntington's Disease, Parkinson's Disease, and dystonia, but there is not good evidence to support its efficacy. Side effects of cannabis include psychosis and anxiety, which can be severe. Here, we provided a summary of the history of cannabis, its pharmacology, and its medical uses.

Cannabis originated in Central Asia, and it is one of the oldest plants used for medicinal purposes. In almost every ancient handbook on plant medicine it is referenced, most commonly in the form of a tincture or a tea (1, 2). Archeological evidence indicates it was cultivated in China for food and fiber as far back as 10000 years ago (3, 4). Clues of the use of cannabis as food and/or medicine have been found in ancient Egyptian mummies (5). It was used in funeral rites by the Scythians and for medicinal applications by the ancient Greeks (6). Cannabis was integral to some religions. For example, in Hindu legend, cannabis (*bhang*) is thought to be the favorite food of the god Shiva, because of its energizing properties (7).

With the spread of cannabis from Asia toward the West, it came into contact with almost every culture. Currently, cannabis can be found in all temperate and tropical climates, except humid, tropical rainforests (8). For hundreds of years, cannabis fibers were used industrially to produce sails for ships, paper, banknotes, and even the first Levi's jeans. When pressed, the oil from the hempseed is very nutritious and a good alternative to fish oil as a source of omega-3-type fatty acids (9).

Until recently, cannabis was grown for fiber on a large scale in most countries, and it was uncommon for cannabis to be abused as a narcotic in the Western world. It was not common knowledge that cannabis had psychoactive properties; because it was mainly selected for their fibrous qualities, it is doubtful that early cultivars contained significant amounts of the psychoactive delta-9-tetrahydrocannabinol (THC). In Europe, the medicinal use of cannabis was first introduced around 1840 by Irish physician William O'Shaughnessy, with the East India Trading Company in India, where cannabis use was widespread (10). Unlike fiber cannabis plants found in Europe, the varieties found in India did contain bioactive compounds. In the intervening decades, cannabis enjoyed a time of popularity throughout Europe and the United States. At the height of its popularity, dozens of medicinal preparations were available, with indications as diverse as menstrual cramps, asthma, insomnia, support of birth labor, migraines, throat infection, and withdrawal from opium use (2).

Difficulties obtaining a supply from overseas and unreliable quality of the plant material made it hard to prepare reliable formulations of cannabis-based medicine. Because quality control was nonexistent, it was difficult to prepare a standardized medicine. Cannabis extract is not water-soluble and cannot be injected, and oral administration is found to be unreliable because of its slow and erratic absorption. Because of these limitations, the medicinal use of cannabis gradually disappeared from Western pharmacopoeias in the period after 1937 (2), as opiates derived from the opium poppy took over the role of herbal cannabis.

The Cannabis Plant

Botanical Description

Cannabis is a wind-pollinated annual plant in which male and female develop as separate plants, but in rare cases, the plant

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develops as a hermaphrodite with male and female flowers on the same plant. It can reach a height of 16 ft (5 m) or more in an outdoor growing season of about 6 months. It can be propagated from seeds and grows vigorously in bright light with well-drained soils (11). Currently, in breeding and cultivation of recreational cannabis, the plants are propagated by cloning, using cuttings of the mother plant. Recently, cannabis cultivars are grown indoors as a high-tech crop under controlled conditions (12).

When the days start to shorten, it triggers the plant to start flowering (13). The female plant then makes several individual flowers arranged in crowded clusters with a large one at the top of the stem and many smaller ones on each branch. Most of the chemical constituents are produced by the female flowers, including cannabinoids and terpenes. Once the flower is fertilized, the plant shifts its metabolic energy to making seeds and away from the biosynthesis of cannabinoids and terpenes. In commercial cultivation, the male plants are usually removed from indoor growing operations to prevent the plants from developing seed (11).

Cannabis Cultivars ("Strains")

There is currently debate about which taxonomy of cannabis should be used—botanical taxonomy, chemotaxonomy, a vernacular taxonomy, and/or recently genetic sequencing (14). Nevertheless, in 2013, the American Herbal Pharmacopoeia classified cannabis as a botanical medicine. Botanically, cannabis has been subclassified based on its phenotypic traits to distinguish the differences between *Cannabis sativa* subsp. *sativa* and *C. sativa* subsp. *indica* cultivars. Both cultivars are a subspecies of *Cannabis sativa L.* (10). Sativa cultivars are phenotypically characterized as being tall with widely spaced branches and long thin leaves; they were originally cultivated for industrial use for fiber, seed oil, and animal feedstuff. In contrast, indica cultivars originated in Southern Asia, are characterized as shorter bushy plants with broader leaves, and were known to be psychoactive (14). Because of extensive breeding programs, most of the cannabis used medically is a hybrid of sativa and indica cultivars. Some researchers recognize a third cultivar, *C. ruderalis*, a smaller, weedy plant originally from Central Russia (10).

Among recreational growers and users of cannabis, a vernacular taxonomy, more accurately a nomenclature, has developed that also uses sativa and indica (14). They often refer to cannabis varieties as "strains." Recreational users and medical patients use this system because it is based on the reported, however not scientifically verified, physical effects that the strains exhibit. According to this common, but scientifically unverified, belief, the effects by sativa "strains" are described as uplifting and energetic and are considered more hallucinogenic. In contrast, indica "strains" are described as calming and are said to cause relaxation and stress relief (15). To what extent the two classification systems, the botanical taxonomy and the vernacular nomenclature, overlap has yet to be investigated (16–18).

Cannabinoids and Terpenes

Cannabis' glandular hairs, which are concentrated around the female flowers, are called trichomes. They excrete a sticky resin that accumulates in droplets at the tip of each hair (19), containing the pharmacologically active compounds, particularly cannabinoids and terpenes. In 2016, Aizpurua-Olaizola et al. identified 554 compounds in cannabis including 113 cannabinoids and 120 terpenes (20).

Cannabinoids.—Cannabinoids are fatty compounds that are typical for the cannabis plant, although some of them can be found in other plants (21, 22). Our body makes cannabinoids as well, called endocannabinoids (23). Cannabinoids can also be synthesized, of which nabilone, a registered cannabinoid medicine, is an example (24). There are 113 cannabinoids found in cannabis plants (20). The two main cannabinoids are THC and cannabidiol (CBD). THC is the main psychoactive compound found in cannabis (12, 25, 26). CBD does not induce a high feeling and may instead counteract some of the side effects of THC (27); it has also been shown to help with anxiety and epilepsy (28–30). Other notable cannabinoids found in cannabis are cannabichromene, cannabigerol, cannabinol (CBN), tetrahydrocannabinolic acid, and tetrahydrocannabivarin (THCV).

Terpenes.—Terpenes are compounds that create the smell and taste of a plant. Some of the most commonly identified terpenes in cannabis plants are α-pinene, myrcene, limonene, β-caryophyllene, and linalool. Terpenes have been shown to bind to receptors in animal models, meaning that they could also cause effects (22). Other than standalone effects, there are effects that could cause a drug to work better or worse or to work longer or shorter, or the terpene could copy a drug's effect (22). Taken together, cannabinoids and terpenes have been associated with the Cannabinoid-Terpene Entourage Effect (31–33), which can be described as how the various compounds in cannabis interact with each other to produce a specific effect that is greater than if the individual compounds were taken alone.

Other compounds.—Cannabis contains other compounds besides cannabinoids and terpenes; Brenneisen et al. list hydrocarbons, nitrogen-containing compounds, carbohydrates, flavonoids, fatty acids, noncannabinoid phenols, alcohols, and esters, as well as many others (34). Although some of them influence the smell of cannabis, it is unclear if, and to what extent, these compounds influence the effects of cannabis.

Cannabinoid Pharmacology and the Endocannabinoid System

The Endocannabinoid System

A new signaling system within the body was first discovered in the early 1990s and opened a whole new field of research and discovery. This system, known as the endogenous cannabinoid signaling system, or endocannabinoid system (ECS), is involved with homeostasis of the body in which it affects a wide range of physiological actions. It is a neuromodulatory system, meaning that a given neuron uses one or more chemicals to regulate diverse populations of neurons. This contrasts with synaptic transmission, in which only one partner neuron is targeted. The ECS is composed of cannabinoid receptors, endogenous ligands (molecules that bind to the receptors and that can induce or block actions), and enzymes that produce, transport, and/or degrade those ligands. The ECS was discovered in the early 1990s with the discovery of the endogenous cannabinoid anandamide (AEA) and the subsequent cloning of the cannabinoid receptor type 1 in 1990 and type 2 in 1993 (35, 36). Regulation of feeding is believed to be the function of the ECS in primitive organisms; for example, De Petrocellis showed that the Hydra

(*Cnidaria Hydrozoa*) used the selective cannabinoid binding sites and the endogenous cannabinoid receptor ligand, AEA (37). The rudimentary nervous system of the Hydra was described in 1919 by Parker and has been found in fossils dated more than 500 million years old (37, 38). In higher organisms, like mammals, the endocannabinoid system's primary function is believed to be controlling homeostasis, or a balance of the systems in the body, with its different mechanisms and interactions, especially during illness (39).

Receptors are binding places in the body that receive chemical signals leading to effects. There are many different types of receptors, and the cannabinoid receptors belong to the large family of the so-called G-protein coupled receptors (GPCRs). Currently, two cannabinoid receptors have been identified and cloned (36, 40), although there is debate about additional receptors (41, 42). The cannabinoid receptor type 1 (CB_1) is predominantly present in the central nervous system (brain and spinal cord), where it regulates functions when under the influence of cannabis, including sleep, appetite, perception of time, short-term memory, and coordination (43). In fact, CB_1 is the most abundant GPCR known to be present in the brain (44). The cannabinoid receptor type 2 (CB_2) is generally present on cells of the immune system, where it can influence pain, inflammation, and tissue damage (45). Not all cannabinoid effects can be explained by cannabinoid receptor binding alone; some effects are caused through other mechanisms, for example, binding to the serotonin receptor, β-andrenergic receptor, and μ-opioid receptor (46, 47).

Endocannabinoids are endogenous compounds that bind to cannabinoid receptors. These compounds are fatty compounds that are produced by the body versus exogenous compounds that originate outside the body. A variety of compounds with endocannabinoid activity have been isolated or synthesized over the years. The best-studied endocannabinoids are AEA (Ananda is Sanskrit for "bliss"; 35) and 2-arachidonylglycerol (2-AG; 48, 49).

Several pathways have been identified for the synthesis and degradation of endocannabinoids, and they are highly redundant (50). Endocannabinoids exist intracellularly in the plasma membranes of neurons. They are released by biochemical pathways involving enzymes. The degradation of endocannabinoids involves the reuptake of the endocannabinoid into the presynaptic cell, followed by rapid hydrolysis of the amide or ester bonds by specialized enzymes (51).

Cannabinoids' Mode of Action

Endocannabinoids are described as retrograde transmitters because they commonly travel backward against the usual synaptic transmitter flow, i.e., they are released from the postsynaptic cell and act on the presynaptic cell, where the target receptors are densely concentrated. Several cannabinoids derived from plants, phytocannabinoids, interact with the ECS by binding with one or more of the cannabinoid receptors. Some effects of phytocannabinoids may be therapeutic, but in other circumstances, unwanted effects may occur. One of the most well-known effects is caused by the phytocannabinoid THC binding, which stimulates the central CB_1 receptors and results in the user feeling intoxicated or "high." Besides THC, other cannabinoids can have an affinity for CB_1 and/or CB_2. Depending on their concentrations, some of these act as partial agonists (e.g., CBN, Δ8-THC, CBD), whereas others act as antagonists (e.g., THCV; 52, 53).

The terpenes found in cannabis may influence the overall therapeutic effect/negative effects in several possible ways, for example, by helping cannabinoids to penetrate the blood–brain barrier more easily or by altering liver metabolism of the cannabinoids, resulting in either a subtherapeutic or toxic "dose" (47). In addition, some terpenes may even compete directly with cannabinoids at the receptor level. Take, for example, β-caryophyllene, a major terpene found in cannabis; it selectively binds to the CB_2 receptor at very low concentrations, acting as a full agonist (54). Some studies show that whole cannabis plant preparations (containing the various cannabinoids and terpenes) may have superior therapeutic effects when compared with purified cannabinoids alone (47). This could indicate that, for some therapeutic uses, cannabis constituents may work in a synergistic manner commonly known as the entourage effect mentioned in *Terpenes*.

Receptor binding.—An agonist is a chemical/drug that binds to a receptor and causes it to activate and produce a biological response; a partial agonist binds to the receptor but only causes a partial effect. Conversely, an antagonist blocks the action of the agonist, and an inverse agonist causes an opposite action to that of the agonist. For a graphical representation, *see* Figure 1.

Cannabinoid Clinical Pharmacology

When a drug is introduced into the body, two things happen. One is that the drug influences the body; this is

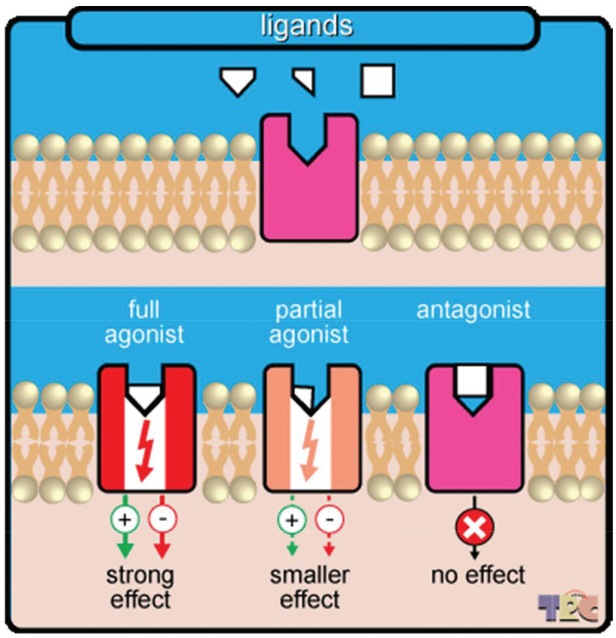

Figure 1. Graphical representation of receptor ligands. Upon binding to a receptor, a full agonist, or agonist, will induce an effect (bottom left). A partial agonist gives a smaller effect as compared with a (full) agonist (bottom middle). An antagonist binds to the receptor but does not have an effect: It blocks the receptor and can prevent other ligands from binding to the receptor (bottom right). Image taken with permission from TRC Pharmacology Database (https://coo.lumc.nl/TRC/). Color images are available online at http://aoac.publisher.ingentaconnect.com/content/aoac/jaoac.

known as pharmacodynamics. The other thing that happens is the body acts on the drug, known as pharmacokinetics. The pharmacokinetics of drugs, including medicinal compounds, can be broken down into roughly four phases, commonly referred to as "Absorption, Distribution, Metabolism, and Elimination" (ADME). Absorption is the phase immediately following administration, in which the drug goes from the site of administration into the bloodstream. Once the drug is in the blood, it needs to be delivered throughout the body to sites of action and off-target site (usually associated with side effects); this process is known as distribution. To remove the drug/cannabis, the body metabolizes the drug to metabolites to make it more water-soluble (hydrophilic) and therefore making it easier to excrete. This usually happens in the liver. Once the drug/cannabis has been changed to a form that can easily be removed from the body, it is eliminated, for example, via urine or feces.

THC pharmacokinetics.—Although the pharmacokinetics of THC is well known, there are limited data on other cannabinoids found in cannabis. We will therefore describe the ADME of THC.—(*1*) *Absorption*.—The administration form used determines the absorption rate of THC into the bloodstream. In general, THC is almost instantly absorbed after inhalation, within minutes, although after oral ingestion, the absorption can take up to an hour or more before a significant amount of THC is absorbed from the gastrointestinal tract (2, 55–57).

(*2*) *Distribution*.—Because THC is very lipophilic in nature, THC and its metabolites rapidly distribute to fatty tissues and highly vascularized organs, such as the brain (58, 59). Because of this lipophilicity, THC accumulates and is stored in the body fat, where it is slowly released back into the blood to be metabolized (57).

(*3*) *Metabolism*.—In humans, THC is mainly metabolized via the cytochrome P (CYP)450 enzyme system by hydroxylation and oxidation by the enzyme CYP2C9, and to a lesser extent, CYP2C19 and other enzymes (60, 61). CYP450 metabolism primarily takes place in the liver (60, 61). It should be noted that the metabolite 11-hydroxy-THC (11-OH-THC) is also psychotropic and may be more potent than its parent molecule THC, while also having a similar kinetic profile (25). In contrast, the subsequent metabolite 11-carboxy-THC (11-COOH-THC) is not psychotropic. 11-COOH-THC is further converted into its final glucuronide form, where it is excreted. When THC is inhaled, by either smoking or vaporizing, it largely avoids the process of first-pass metabolism—which is when a drug is absorbed from the intestines and is immediately metabolized by the liver before it reaches the systemic circulation (blood)—because the THC is absorbed directly into the blood from the lungs. Because of the differences in absorption (see above), the ratios at which THC metabolites are seen in the body after administration are largely dependent on the administration route. This can have implications for effect strength. For example, a person eating an edible cannabis product, who is very efficient at metabolizing THC to 11-OH-THC, may have a more pronounced "high" from the edible, because their body makes more of the more potent metabolite, 11-OH-THC, after consuming an edible. Conversely, if the same person inhaled a joint, because the THC enters the blood directly and goes straight to the brain, the effect of the more potent metabolite is mitigated.

(*4*) *Elimination*.—THC is extensively metabolized by the body; as a result, only negligible amounts of THC are excreted as its unchanged form. Of an oral dose, about 15–30% THC is excreted in urine as metabolites with less than 0.05% as unchanged THC, and about 30–65% metabolites are excreted in the feces, with less than 5% as unchanged drug. Of all the metabolites of THC, 11-COOH-THC is the major metabolite identified in both urine and feces, in both its native and glucuronidated form (62). The half-life of THC, which is defined by the time it takes to remove half of the drug from the blood (plasma), and its metabolites can be several days. The slow elimination from the plasma can be explained by redistribution from peripheral tissues, such as the fatty tissue discussed above, into the bloodstream. Following single dose administration, low levels of THC metabolites have been detected for more than 5 weeks in the urine and feces (63). It should be noted that this terminal half-life is independent from the route of administration.

Cannabinoid pharmacodynamics.—Pharmacodynamics can occur in various ways, i.e., through cellular disruption, chemical reactions with downstream effects, interaction with enzyme proteins, interactions with carrier proteins and ion channels (transporters), and binding to receptors (64). Cannabis can produce a variety of pharmacological effects on the body, with THC being the most well-studied cannabinoid that causes pharmacological effects. Cannabis exerts most of its pharmacological effects by binding and interacting with the CB_1 and CB_2 receptors (2, 55, 56). THC is a partial agonist of both CB_1 and CB_2 receptors (55, 56). When an agonist binds to a receptor, it activates the receptor to elicit a response. A ligand can also bind to a protein and cause a change in the protein that then makes it less receptive to the effected ligand, which is known as an allosteric effect. For a drug to have an effect, it must reach a site of action, and, in our example, THC must reach the brain to produce the high (65). To reach the target site, drugs are moved across cell membranes in both directions (into and out of cells), usually by transporters; therefore, changes in the drug transporters, either by drug–drug interactions or genetics, can affect the effects of cannabis. Many of the effects produced by cannabis are used to treat a variety of illnesses which we will discuss in further detail later (66).

Cannabinoid safety and tolerability.—Although cannabinoids can cause both euphoric and therapeutic effects, there have been a few studies that indicated cannabis use can also induce schizophrenia, psychosis, and anxiety in healthy individuals who are sensitive to these conditions (67, 68). Unlike the case with opioids, which can cause lethal respiratory depression upon overdose, there have not been any reports on human lethal overdosing with cannabis (69, 70). This is because cannabis, unlike alcohol and opioids, only minimally interacts with the part of the brain involved in respiration. With alcohol and opioid overdose, the brain stops sending a signal to breathe; this does not happen with cannabis (71). However, just because it is very hard to overdose on cannabis does not mean cannabis is a "safe" drug; in patients with high risk factors for heart attacks, cannabis can trigger a heart attack, fatal or otherwise (72, 73). Likewise, it has been shown that cannabis can lead to psychosis and schizophrenia in patients with pre-existing psychotic disorders (74, 75). It has been shown that long-term cannabis use has been associated with a decline in cognitive function; however, after a few days of abstinence, there seems to be a reversal of this decline (76, 77).

Medical Indications for Cannabis Use

Indications with Evidence that Cannabis has Some Efficacy for Treatment

Nausea and vomiting.—Researchers have found that when a sublingual mixture containing equal parts of THC and CBD was added to the standard antiemetic (antivomiting) therapy, it improved the nausea in patients undergoing chemotherapy. One study used a commercial product undergoing U.S. Food and Drug Administration (FDA) approval, nabiximols (Sativex), a sublingual spray that contains THC:CBD in a 1:1 ratio (78). In that study, researchers showed that 71.4% of patients in the treatment group had a complete resolution in their nausea and vomiting, and in the placebo group, 22.2% had complete response. In another study (79) that used National Institute of Drug Abuse–sourced cannabis (900 mg cannabis cigarettes containing 1.93% THC), it was shown that 14 of 15 patients had a reduction in nausea and vomiting in the THC group when compared with the placebo. They also showed a relationship between the blood concentration of THC and effectiveness; the higher the concentration of THC in the blood, the lower the incidence of nausea and vomiting. Although 72% of patients had nausea and vomiting in the placebo group, there was a reduction in nausea and vomiting to 44, 21, and 6% in the three groups defined on the THC plasma (a part of blood) concentration groups (<5, 5–10, and >10 ng/mL, respectively; 79).

Pain.—(*1*) *Pain associated with multiple sclerosis (MS)*.—Researchers found that cannabis-based medicines are probably effective for treating the neuropathic pain and painful spasms associated with multiple sclerosis (80). However, it is unclear if smoked marijuana is effective for reducing MS pain (80). Researcher Langford et al. concluded that more research is needed; their study had mixed results. It has also been shown that cannabis-based medicines reduced the patient-reported spasticity associated with MS (81, 82). In the study by Wade et al., there was a 31.2-point reduction in patient-reported spasticity versus an 8.4-point reduction in the placebo group (81).

(*2*) *Neuropathic pain*.—Cannabis has been found to treat neuropathic pain associated with diabetes, human immunodeficiency virus (HIV), and other causes. Wallace et al. (83) found a dose-dependent reduction in pain intensity in response to inhaled cannabis in patients with diabetic peripheral neuropathy. However, in a study by Selvarajah et al. using a commercial oral-mucosal spray, nabiximols, patients with diabetic neuropathy showed no improvements (84). In another study by Abrams et al. (85), HIV-positive patients found relief from pain by smoking one cigarette of cannabis flower containing 3.56% THC three times per day. Most other studies on neuropathic pain related to other causes have been performed with nabiximols (Sativex) containing THC:CBD in equal ratios and generally show positive results (86–88).

(*3*) *Chronic pain related to cancer*.—Cannabis can be used to treat chronic pain associated with cancer and other causes. Studies generally suggested improvements in chronic pain measures associated with taking cannabis in cancer patients (89, 90). Most studies have been performed with nabiximols (Sativex) containing THC:CBD in a 1:1 ratio and generally show positive results (90, 91). One study in cancer patients had mixed results but was overall favorable; the low-dose group achieved a 26% improvement in pain compared with the baseline (91). It is unclear if whole-flower cannabis or edibles will be as effective, more effective, or less effective. However, one study of whole-flower cannabis (3.56% THC) smoked showed reduced daily pain in HIV patients with sensory neuropathy (85).

Insomnia

Insomnia is a multifaceted disorder. Some patients experience insomnia because they have another condition that makes it difficult to sleep. For example, a patient with chronic pain may have difficulty falling asleep; this is an indirect effect of pain on sleep. Contrast this with a patient who has a job that requires them to get up early in the morning and would like help falling asleep; this is a direct effect on sleep.

Cannabis products such as nabiximols (Sativex) were associated with a greater average improvement in sleep by targeting indirect effects (89). In a study by Russo et al. (92), they summarized the effect of nabiximols on numerous studies looking at treating various conditions that also measured the effect on sleep patterns. They summarized that in studies in 2000 subjects with 1000 patient years of exposure, it demonstrated marked improvement in patient-reported sleep parameters in patients with a wide variety of pain conditions (92). In a safety follow-up study, about 40% of subjects attained good-to-very-good sleep quality with maintenance of up to 2 years, indicating no or limited tolerance (92). In a publication by Bonn-Miller et al. (93), they observed medical-cannabis patients with a diagnosis of post-traumatic stress disorder (PTSD); those with a higher PTSD score were more likely to use cannabis to improve sleep, and they used it more frequently. Problems with interpreting this study, however, include that the patients in the study came from one dispensary in San Francisco, and they did not describe the cannabis products used (93).

Anxiety

There is limited evidence that CBD is effective in the treatment of anxiety symptoms (28). In a study by Bergamaschi et al., they showed that patients with social anxiety disorder treated with oral capsules of 600 mg CBD had lower anxiety measured by a reduction of 16.5 on a 100-point scale in a simulated public speaking test (29). Other studies looked at the effect of oral CBD (400 or 600 mg) on anxiety using brain-imaging studies and subjective measures of anxiety symptoms; compared with a placebo, CBD decreased subjective anxiety in subjects given THC (94–96). It should be noted that cannabis could actually cause anxiety in some users, especially naïve ones (97, 98).

Loss of Appetite

There is limited evidence that oral THC is effective in increasing appetite in HIV-positive patients. (28) In one study by Haney et al. (99), oral THC increased daily caloric intake, weight gain, and the number of times the patients ate per day. It was found that the higher the dosage, the larger the weight gain. The individuals in the group that was treated with the highest dosage (four times a day of 10 mg THC, as dronabinol) had a 2.2 lb (1 kg) increase in weight after 4 days of treatment (99).

It is unknown for how long this weight gain lasted. In the same study, similar beneficial effects were found for a treatment with smoked cannabis.

Tourette's Syndrome

There is limited evidence that THC capsules are an effective treatment for improving symptoms of Tourette's syndrome (28). Case reports (reports written about individuals instead of being randomized, blinded studies) have suggested that smoking cannabis can reduce tics and that the therapeutic effects of cannabis might be due to anxiety-reducing properties of cannabis rather than to a specific antitic effect (100, 101). Two small trials, described in four papers, which were not of good quality, provide limited evidence for the therapeutic effects of THC capsules on tic severity and global clinical outcomes. On a 0–6 severity scale, symptoms were improved by less than 1 point (102–105). A recent study by Abi Jaoude et al. (106) showed that patients who smoked or vaped cannabis had an average of 60% reduction in tics as measured by the Yale Global Tic Severity Scale. The patients also reported improvement in comorbid symptoms with cannabis including obsessive-compulsive symptoms, attention, impulsivity, anxiety, irritability, rage outbursts, and sleep (106).

Post-Traumatic Stress Disorder

Cannabis can be used to treat PTSD symptoms including insomnia and nightmares. In an open-label pilot study by Fraser (107), 34 (72%) patients experienced total cessation or lessening of severity of nightmares (28 patients had total cessation of nightmares and 6 had satisfactory reduction). In a follow-up double-blind treatment study by Jetly et al. (108), they showed that after starting nabilone (an oral synthetic THC) treatment, 7 out of 10 subjects (70%) scored nightmare reduction as very much improved or much improved, compared with 2 out of 9 (22%) on placebo as scored on the Clinical Global Impression of Change, a tool used by clinicians to measure changes in patients' symptoms (108). They did not see any effect on sleep quality (108). Cameron et al. did a study that showed significant improvement in PTSD-associated insomnia and nightmares. Also, in contrast to the study by Jetly, the subjects had an increase in the number of hours slept (mean 5.0 h pretreatment versus 7.2 h post-treatment) as well as fewer nightmares (mean 5.2 pretreatment versus 0.9 post-treatment; 109). The authors noted that side effects, such as psychosis (in patients with preexisting psychotic disorders), sedation, dry mouth, and feeling stoned, were more common in cannabis-naïve subjects and that therapy should be initiated at the lowest possible dose and titrated slower than in cannabis-experienced users (109). Roitman et al. (110) performed a study of oromucosal THC, THC dissolved in olive oil given twice a day and placed under the tongue; all measures assessed in this study showed improvement after treatment compared with the baseline. Tools administered by clinicians showed significant improvement in sleep quality and reduced frequency of nightmares (110). In addition, patient self-reported tools showed improvement in reducing nightmare frequency (110).

Epilepsy

Various studies have demonstrated the effectiveness of CBD, and on June 25, 2018, the FDA approved EPIDIOLEX®, an oral solution of cannabidiol, for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older. Examples of studies showing effectiveness in epileptic seizures include a study that demonstrated CBD to reduce seizure frequency in children and young adults with highly treatment-resistant epilepsy (30, 111–113). Another study by Devinsky et al. (30) reported that the median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with CBD, as compared with a decrease from 14.9 to 14.1 with placebo in patients with Dravet syndrome in the age range of 2.3–18.4 years old. The most frequently occurring side effects were diarrhea, vomiting, fatigue, somnolence, and abnormal results on liver-function tests, but it was otherwise well tolerated (30). In one older review of four studies looking at children with treatment-resistant epilepsy, half the studies showed a reduction in seizure frequency, and the other half showed no improvement over placebo, but all these studies had limitations (112).

Indications with Evidence that Cannabis Has No Proven Efficacy for Treatment

There are other indications that have been investigated to see if cannabis would be a useful treatment. To date, the studies looking at Huntington's Disease, Parkinson's Disease, and dystonia have provided insufficient evidence to support that cannabis is effective (28, 114–119). Based on reviews of the scientific literature, there is some evidence to prove that THC is an effective treatment of glaucoma (28, 120–123).

Conclusions and Recommendations

In conclusion, cannabis has a long history of being used medicinally. From its start as an industrial fiber plant, cannabis is increasingly being recognized for its medical properties. Cannabis contains hundreds of compounds, including cannabinoids and terpenes, the most prominent cannabinoid being THC, with CBD gaining more importance in recent research. Although there is some research on the effects of THC on the body and how the body processes THC, there still needs to be more research on the other cannabinoids and terpenes to elucidate their individual and combined pharmacokinetics and pharmacodynamics. To date, there are numerous indications for cannabis use with scientific evidence of its efficacy, including nausea and vomiting, pain, patient-reported MS spasticity symptoms, sleep, anxiety, appetite and weight loss, Tourette's Syndrome, PTSD, and epilepsy. Conversely, dementia, Huntington's Disease, Parkinson's Disease, dystonia, depressive symptoms, and glaucoma have limited evidence to support cannabis is not effective, or have a lack of evidence for efficacy. This relatively new field of research, limited by prohibitive regulations because of political reasons, needs more intense study, and we believe future research directions need to include more reliable and effective administration methods; safety of (individual) cannabis constituents when heated and inhaled; safety in pregnancy, lactation, and consequences for infancy; application in a variety of (psychiatric) disorders; a better understanding of factors influencing effect strengths and profiles including age, sex, and genetic predispositions; and understanding how synthetic compounds can safely and effectively act on the ECS.

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