Medical Marijuana and Other Cannabinoids

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty
Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for physicians, nurses, physician assistants, pharmacists, social workers, therapists, and counselors in the primary care setting involved in the care of patients who use or who are candidates for the therapeutic use of marijuana or other cannabinoids.

Accreditations & Approvals
JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

As a Jointly Accredited Organization, NetCE is approved to offer social work continuing education by the Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) program. Organizations, not individual courses, are approved under this program. Regulatory boards are the final authority on courses accepted for continuing education credit.

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This course is considered self-study, as defined by the New York State Board for Social Work. Materials that are included in this course may include interventions and modalities that are beyond the authorized practice of licensed master social work and licensed clinical social work in New York. As a licensed professional, you are responsible for reviewing the scope of practice, including activities that are defined in law as beyond the boundaries of practice for an LMSW and LCSW. A licensee who practices beyond the authorized scope of practice could be charged with unprofessional conduct under the Education Law and Regents Rules.

A complete Works Cited list begins on page 35.

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This course is considered self-study by the New York State Board of Mental Health Counseling.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to earn credit toward the CME and Self-Assessment requirements of the American Board of Surgery's Continuous Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABS credit.

This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 5 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

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NetCE designates this continuing education activity for 5 ANCC contact hours.

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 6 hours for Alabama nurses.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 5 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-20-089-H04-Pand JA4008164-0000-20-089-H04-T.

Social workers completing this intermediate-to-advanced course receive 5 Clinical continuing education credits.

NetCE designates this continuing education activity for 3.5 NBCC clock hours.

NetCE designates this continuing education activity for 5 continuing education hours for addiction professionals.

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In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 07/29/2025); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2025); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

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Special Approvals
This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor
The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

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Course Objective
The purpose of this course is to provide healthcare professionals with unbiased and evidence-based information regarding the use of marijuana and other cannabinoids for the treatment of medical conditions.

Learning Objectives
Upon completion of this course, you should be able to:

1. Recall the history of therapeutic cannabis use.
2. Outline the function of the endocannabinoid system.
3. Analyze the pharmacology of exogenous cannabinoids in clinical or experimental use.
4. Discuss potential side effects and areas of safety concern when medicinal cannabis and other cannabinoids are used.
5. Describe the potential therapeutic benefit and appropriate indications for the medical use of marijuana and other cannabinoids.
6. Identify primary indications, side effects, chronic effects, and contraindications to therapeutic cannabinoid use.

Pharmacy Technician Learning Objectives
Upon completion of this course, you should be able to:

1. Describe the background and pharmacology of marijuana and other cannabinoids.
2. Outline factors affecting the medical use of marijuana, including risk factors, benefits, and indications.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Cannabis, or marijuana, was introduced to the United States as a medicinal product in the mid-1800s and was widely prescribed by physicians as a therapeutic until 1937, when sanctions were levied against medical or recreational use and physician prescribing. Prohibition culminated in 1970 with passage of the Controlled Substance Act, which formalized the criminalization of marijuana possession or use, regardless of quantity or context. Despite its illegal status, public demand for medical access led to the legalization of marijuana for medical use in California in 1996; as of 2020, voters in an additional 33 states and the District of Columbia have followed suit. In addition, 11 states, including California, have also legalized recreational cannabis use [1]. Popular demand and legal access to medical marijuana began despite the lack of well-designed randomized clinical trials (RCTs), the result of decades-long federal law enforcement obstruction. However, numerous RCTs have been published since 2000, markedly clarifying appropriate indications and contraindications.

In aggregate, the published clinical research strongly supports medical marijuana use in alleviating chronic neuropathic or cancer pain, spasticity, nausea and vomiting, weight loss and wasting syndrome associated with chronic debilitating conditions, and potential opioid dose reduction with analgesic enhancement as co-therapy in long-term opioid analgesic use [2; 3; 4]. Possible efficacy is suggested in fibromyalgia, post-traumatic stress disorder (PTSD), seizure disorders, and irritable bowel syndrome/Crohn disease. Contraindications include a personal or family history of psychoses; age younger than 18 years; and pregnancy or breastfeeding. Medical marijuana users are unlikely to develop negative immune effects, cognitive impairment persisting beyond the acute dose, or psychotic disorder when appropriately screened. Lifetime addiction prevalence is 1.5% to 9% in recreational users and unknown in medical users [5; 6]. However, about 11% of recreational marijuana users report daily use, compared with one-third of medical marijuana users [7]. In states with medical marijuana laws, 83% use cannabis recreationally and 17% use it for medical reasons.

The sociopolitical controversy surrounding non-medical marijuana use frequently spills over into discussion of medical marijuana, obscuring objective discussion of the scientific basis. Value judgments play an even greater role in legal and regulatory decisions related to marijuana and other drugs that are used for recreational purposes [8]. Kalant offers two important suggestions to physicians weighing medical marijuana benefits/risks [2]. First, medical use and non-medical use are unrelated. For example, heroin can be legally prescribed in Canada to relieve suffering in patients terminally ill with cancer. No one has suggested heroin should therefore be available for non-medical use, and to think differently about marijuana lacks a rational basis. Second, marijuana is not used as first-line therapy for any indication. Instead, its greatest therapeutic potential comes from treating patients with chronic conditions refractory to standard therapies [2]. The initial primary concerns of the Institute of Medicine (IOM) over medical marijuana were possible pulmonary harms and inability to control and replicate drug concentrations, but these are being resolved by availability of vaporization and, in Canada, Holland, and some U.S. states, by large-scale cannabis growing with quality, purity, and reliability consistent with pharmaceutical standards [8].

Despite substantial progress in the scientific understanding of cannabis mechanisms and the available outcomes of rigorously designed RCTs, this information is not reaching healthcare providers who practice in states legally permitting medical marijuana use [9]. This information transfer is essential to elevate the knowledge base of benefits, risks, and indications for medical marijuana and to improve patient interactions when this controversial topic is raised [9].

Provider demand for this information was captured by a survey of Colorado family practice physicians, of whom 82% endorsed including medical marijuana education in family practice residency training and 92% expressed interest in medical marijuana continuing education. However, only 19% agreed that physicians should recommend medical marijuana to their patients. One concerning finding was the significantly greater influence of news media in the decision to not recommend medical marijuana to patients. While these results were based on a 30% response rate to the surveys, they indicate that physicians are uncomfortable recommending medical marijuana but recognize the importance and unmet need of education and training on its clinical use [10]. In other words, lack of education is a fundamental cause of healthcare professionals' reluctance; more specifically, this results from knowledge deficits in the therapeutic value, appropriate indications, contraindications, dosing, and benefits/risks balance in medical marijuana, all of which can be addressed by continuing education [2; 11].

The urgent need for medical marijuana continuing education is underscored by findings that primary care providers refusing medical marijuana involvement has led to naturopathic doctors (NDs) filling this void by opening medical marijuana authorization practices in states granting NDs this function. Prescribers' discomfort is also influenced by fears over revocation of their license to prescribe controlled substances, with medical marijuana legally allowed in some states while remaining a violation of the federal Controlled Substance Act [12]. This concern is similar to the widespread fear over opioid analgesic prescribing, that doing so heightens risk of law enforcement or regulatory scrutiny and possible sanction or prosecution. This barrier to patient care is amenable to educational intervention by presentation of the potential benefits and factual reassurance that by authorizing medical marijuana consistent with state laws, the risks to one's licensure are essentially nonexistent. Unlike opioid prescribing, no U.S. physician has been successfully prosecuted or sanctioned for authorizing medical marijuana consistent with their state laws (as of 2020) [11]. In fact, a congressional spending bill (passed in 2017) prohibits the U.S. Drug Enforcement Administration (DEA) from spending any money to block states from "implementing their own laws that authorize the use, distribution, possession, or cultivation of medical marijuana," which, as affirmed by the Supreme Court in 2016, prevents the Department of Justice from prosecuting anyone in states with legal marijuana [13].

Botanical cannabis is the focus of this course, and while pharmaceutical cannabinoids are also discussed, the two should not be viewed as medicinally equivalent. Differences in pharmacologically active constituents and routes of administration result in distinct pharmacologic and clinical profiles [14]. This course will emphasize medical marijuana use in chronic pain because this is the most frequent condition for its use and because the highest proportion of well-designed clinical trials have evaluated efficacy in treating chronic pain [10; 15].

TERMS

The following terms are used often in discussions of medical marijuana use, and these definitions may help clarify the issues being described.

Cannabis: derived from *Cannabis sativa*, the proper name of the marijuana plant. Cannabis is a dioecious species, meaning it has male and female plants. Roughly half the plants grown from seed are female; when not fertilized by males to produce seeds, female plants bear flowering buds called sinsemilla, the part of the plant with highest Δ9-tetrahydrocannabinol (THC) concentration [16].

Marijuana: a synonym and slang term for cannabis, often used when discussing medical use.

Cannabinoid: a category that includes endogenous cannabinoid receptors, their endogenous ligands, and the plant-occurring or synthetic molecules that interact with cannabinoid receptors or their ligands [17].

Δ9-tetrahydrocannabinol: the primary active cannabis constituent. Referred to throughout this course as THC.

HISTORY OF MEDICINAL CANNABIS USE

USE IN ANCIENT CIVILIZATIONS

The evolution of *Cannabis sativa* has been traced to the Central Asian/Himalayan region roughly 36 million years ago [18]. Over time, cannabis spread to all regions with human habitation, reflecting the value placed on its medicinal, spiritual, and dietary utility [19].

The Chinese emperor Shen Nung is believed the first to formally describe the therapeutic properties and uses of cannabis in his 2737 B.C.E. compendium, in which it was recommended for the treatment of malaria, constipation, rheumatic pains, and childbirth and mixed with wine as a surgical analgesic

[20; 21]. Medicinal and religious use achieved great prominence in India around 1000 B.C.E. and was implicitly endorsed by the Hindu religion. Medicinal cannabis became widely used as an analgesic (for neuralgia, headache, toothache), anticonvulsant (for epilepsy, tetanus, rabies), sedative-hypnotic (for anxiety, mania, hysteria), anesthetic and anti-inflammatory (for rheumatism and other inflammatory diseases), antibiotic (for topical use on skin infections, erysipelas, tuberculosis), antiparasitic (for internal and external worms), antispasmodic (for colic, diarrhea), digestive, appetite stimulant, diuretic, aphrodisiac or anaphrodisiac, antitussive, and expectorant (for bronchitis, asthma). During the pre-Christian era, medical cannabis use remained widespread in India and areas of Assyria and Persia. Through the Christian era into the 18th century, it remained extensively used in India and spread throughout the Middle East, Africa, and the Arabian Peninsula, where prominent Arab physicians placed cannabis in their medical compendiums [20; 22].

INTRODUCTION AND WIDESPREAD USE IN WESTERN MEDICINE

Western medicine was introduced to cannabis by a 1839 publication of O'Shaughnessy, a physician who described its successful use in his patients as an analgesic, appetite stimulant, antiemetic, muscle relaxant, and anticonvulsant, and by the 1845 publication of Moreau, a psychiatrist who documented the results of cannabis use in his patients, his students, and himself [20; 21]. Support for medical cannabis use was disseminated by these publications from England and France throughout Europe and North America. Cannabis was entered in the U.S. Dispensatory in 1854, and the first medical conference on cannabis was held in 1860 by the Ohio State Medical Society. By 1900, more than 100 scientific articles on cannabis efficacy had been published in the United States and Europe. Cannabis was usually available as a tincture comprised of plant extract. Aware of the therapeutic potential, researchers worked to resolve its limitations, including lack of water solubility, delayed onset of action (when given orally), variable potency, difficulty in standardized dosing, and individual differences in response. The importance of dose titration was stressed [20; 22]. The late 19th to early 20th century was the pinnacle of cannabis use in Western medicine. Cannabis extracts were marketed by Merck, Burroughs-Wellcome, Bristol-Meyers Squibb, Parke-Davis, and Eli Lilly. The 1924 edition of the influential medical textbook *Sajous's Analytic Cyclopedia of Practical Medicine* listed numerous indications for cannabis, including [20; 22]:

- Sedative or hypnotic: Insomnia, melancholia, delirium tremens, chorea, tetanus, rabies, hay fever, bronchitis, pulmonary tuberculosis, coughs, spasm of the bladder
- Analgesic: Headaches, migraine, eye strain, menopause, brain tumors, neuralgia, gastric ulcer, indigestion, multiple neuritis, pain not due to lesions, dysmenorrhea, chronic inflammation, acute rheumatism, eczema and pruritus, tingling, numbness of gout, dental pain
- Other uses: To improve appetite and digestion associated with "pronounced anorexia following exhausting diseases," dyspepsia, diarrhea, dysentery, cholera, nephritis, diabetes mellitus, vertigo

Many indications are consistent with scientific confirmation, more than 90 years later, of analgesic, antispasmodic, antiemetic, sedative, anti-inflammatory, anticachexic, and antianorexic efficacy.

THE 20TH CENTURY

The psychoactive properties of cannabis were recognized thousands of years ago but were valued mainly as religious adjuncts. Before the mid-20th century, recreational cannabis use was restricted to "fringe" or marginalized groups and the impoverished, for whom it was considered "the opium of the poor" [19]. Its use became increasingly popular in African American and immigrant Hispanic neighborhoods in the United States before 1950.

Cannabis prescribing in the United States significantly declined over the first three decades of the 20th century due to difficulty in developing reliable, standardized preparations; inability to isolate its active constituent; and introduction of effective medications in the areas of primary indication for cannabis. Medical cannabis use was burdened with severe taxation by the Federal Marihuana Tax Act of 1937, and cannabis was removed from the U.S. Pharmacopoeia in 1942 [8]. The American Medical Association (AMA) opposed both acts and testified before Congress that nearly 100 years of medical experience in the United States had demonstrated an irreplaceable therapeutic role for cannabis [23; 24]. Prohibition of medical marijuana culminated with the 1970 Controlled Substance Act (CSA) that categorized marijuana, along with heroin, as a Schedule I substance or CS-I. Drugs with CS-I listing are deemed highly addictive and devoid of medical value or safety. The CSA was a component of the "War on Drugs" launched in 1968, enforced and upheld by the newly established DEA. Possession of a CS-I substance potentially confers severe legal consequences, and possessing small amounts of cannabis has led to the lengthy incarceration of many. Black Americans have been disproportionately arrested and incarcerated for marijuana possession. Despite data showing that drug use is unaffected by severity (or leniency) in drug policy, harsh sentencing of marijuana possession has persisted in some jurisdictions [25]. Prominent groups have petitioned the government to review and reconsider its Schedule I status, including the IOM, the AMA, and the American College of Physicians [24].

Research and clinical interest in cannabis was reignited with identification of the chemical structure for THC in 1964, followed by discovery and cloning of cannabinoid receptors and isolation of the endogenous cannabinoid anandamide in the 1970s to early 1990s [24]. The first sporadic scientific reporting of medical marijuana benefit started in the 1970s, particularly with nausea and vomiting from chemotherapy. As the acquired immune deficiency syndrome (AIDS) epidemic spread through the 1980s, patients increasingly found that marijuana relieved many of their symptoms, particularly wasting symptoms associated with AIDS. A landmark 1999 IOM report described the scientific and clinical basis for supporting medical marijuana use. There were increasing media reports of medical marijuana users subjected to criminal prosecution during this period [8]. These events stimulated media attention and growing public demand for medical access. Despite its illegal status at the federal level, cannabis was reintroduced into medical use in 1996 by popular vote and legislative acts in California. By 2020, 33 states and the District of Columbia had followed suit [1]. (For information on laws pertaining to medical marijuana in your state, visit https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc.) In addition, cannabis is used by millions of patients for medicinal purposes in jurisdictions where it remains illegal for medical use [11]. In opposition to federal law, state medical marijuana programs have received support by official federal statements of cooperative noninterference by the Veterans Health Administration and the U.S. Department of Justice in 2009 [24].

The DEA and National Institute on Drug Abuse (NIDA) are funded by the Office of National Drug Control Policy (ONDCP). Both agencies are guided by ONDCP's agenda and explicit policy goal of a drug-free America. The NIDAs research priority on cannabis harms reinforces its CS-I status by DEA. This long-standing federal obstruction of cannabis efficacy research perpetuated criticism that cannabis lacked scientific evidence of clinical benefit [11]. However, since 2000, advances in research design and evaluation have finally been applied to cannabis research. There are now numerous well-controlled clinical trials that fulfill the highest contemporary standards of scientific evidence. This clinical data, and the findings of preclinical and population-level studies, have greatly clarified the risk/benefit profiles of cannabis in a number of indications, addressed many long-standing safety concerns, defined patient contraindications, and identified the safety outcomes in recreational users that are inappropriate for generalization to medical users [11].

Contributing to this body of evidence was the 1999 founding of the Center for Medicinal Cannabis Research (CMCR) at the University of California, San Diego. The CMCR is the first comprehensive cannabis clinical research program in the United States and was launched with the goal of conducting randomized, placebo-controlled safety and efficacy trials of smoked cannabis in the treatment or management of the diseases and conditions identified by the IOM for which cannabis has highest therapeutic potential [26]. A similar process began in Canada in 2001, with the goal of systematically investigating cannabinoid safety and efficacy through preclinical and clinical trials. This was part of a larger effort by the Canadian government to better understand safe and effective medical cannabis use and was initiated in tandem with a centralized and controlled process of cannabis cultivation and distribution to appropriate medical patients [27; 28]. The Netherlands government established the Office of Medicinal Cannabis (OMC) in 2000 to grow cannabis according to pharmaceutical standards and to implement a supply chain to distribute and dispense cannabis to patients and researchers [29].

THE ENDOGENOUS CANNABINOID SYSTEM

The endogenous cannabinoid system (ECS) is a signaling system that includes cannabinoid receptors, endogenous receptor ligands (termed endocannabinoids), and their synthesizing and degrading enzymes [30]. Core functions of the ECS have been described as "relax, eat, sleep, forget, and protect," shorthand for the diversity of processes involving the ECS [31]. The ECS regulates neuronal excitability and inflammation in pain circuits and cascades and also helps regulate movement, appetite, aversive memory extinction, hypothalamic-pituitary-adrenal (HPA) axis modulation, immunomodulation, mood, wake/sleep cycles, blood pressure, bone density, tumor surveillance, neuroprotection, and reproduction. The so-called "runner's high" and the effects of osteopathic manipulative therapy and electroacupuncture are mediated by the ECS [32; 33].

The ECS is a system common to all vertebrates and many invertebrates and has been present in living organisms as far back as 600 million years. In the invertebrate species *Hydra vulgaris*, a primitive evolutionary throw-back to several hundred million years, feeding is mediated by the ECS. This discovery underscores the essential pro-survival function of the ECS that long pre-dates mammalian evolution, where the more recently evolved hypothalamic system regulates the survival function of appetite [28; 34].

CANNABINOID RECEPTORS

CB1 Receptors

CB1 receptors are the most abundant G-protein-coupled receptors in the brain and are expressed at lower densities in many peripheral tissues. CB1 receptors solely mediate the psychotropic and behavioral effects of cannabinoids and regulate several peripheral processes, such as energy homeostasis, cardiovascular function, and reproduction [30; 35].

CB1 distribution in the brain matches the known pharmacodynamic effects of cannabinoids; CB1 activation prominently modulates cognition and memory, perception, control of motor function, and analgesia [36]. The location and relative density of CB1 receptors in the brain and function mediated by CB1 activation are outlined in ***Table 1*** [37; 38; 39; 40].

CB2 Receptors

CB2 receptors are sparsely expressed in the central nervous system (CNS) but highly expressed in immune cells, where they play an important role in regulating immune function and inflammation. Their activation modulates immune cell migration and cytokine and chemokine release, and CB2 receptor expression on CNS microglia may explain cannabinoid efficacy in reducing cytokine-mediated neuroinflammation [30; 41; 42; 43].

CB1 RECEPTORS IN THE BRAIN	
Brain Region	**Function**
Highest CB1 density	
Substantia nigra	Reward, addiction, movement
Cerebellum	Motor control and coordination
Globus pallidus	Voluntary movements
Caudate nucleus	Learning and memory system
Moderate CB1 density	
Cerebral cortex	Decision-making, cognition, emotional behavior
Putamen	Movement, learning
Amygdala	Anxiety and stress, emotion and fear, pain
Hippocampus	Memory and learning
Lower CB1 density	
Hypothalamus	Body temperature, feeding, neuroendocrine function
Minimal or absent CB1 density	
Brain stem	--
Medulla	
Thalamus	
Source: [37; 38; 39; 40]	*Table 1*

Other Endocannabinoid Receptors

In addition to CB1 and CB2 receptors, endocannabinoids are thought to bind several other molecular targets. These include a third presumed cannabinoid receptor, GPR55 (sometimes termed CB3), the transient receptor potential cation channel subfamily V member 1 (TRPV1), and a class of nuclear receptors/transcription factors known as the peroxisome proliferator-activated receptors (PPARs) [30].

Endogenous Cannabinoids Receptor Ligands

Anandamide and 2-arachidonoyl glycerol (2-AG) are the two primary endogenous cannabinoid receptor ligands.

Anandamide (Arachidonoyl Ethanolamide, AEA)

Anandamide was the first endogenous cannabinoid identified by researchers and was assigned its name after *ananda*, the Sanskrit word for "bliss" [37]. Anandamide is derived from arachidonic acid following synthesis from membrane phospholipid precursors. At CB receptors, anandamide acts as a partial agonist, with slightly higher binding affinity at CB1 versus CB2 [36]. Anandamide is hydrolysed by the enzyme fatty-acid amide hydrolase (FAAH) as the primary metabolic pathway [44].

2-Arachidonoyl Glycerol (2-AG)

2-AG binds essentially equally to both CB receptors (with slightly higher CB1 affinity) and possesses greater overall potency and efficacy than anandamide at both CB receptors [36]. 2-AG is an arachidonic acid derivative synthesized by the same process as anandamide. The metabolic pathway of 2-AG predominantly involves monoacylglycerol lipase (MGL or MAGL) [36; 44].

Additional Endocannabinoids

Other endogenous molecules have been identified that mimic endocannabinoid effects. These include 2-AG ether (noladin ether), *N*-arachidonoyl dopamine (NADA), virodhamine, *N*-homo-γ-linolenoylethanolamine (HEA), and *N*-docosatetraenoylethanolamine. Although the molecules palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) bind to PPARs instead of cannabinoid receptors, their action potentiates anandamide effect by inhibiting FAAH (the enzyme that degrades anandamide) and by direct allosteric effects on other receptors. The sum of these effects is referred to as the "entourage effect" [45; 46; 47]. PEA has become a research focus, with a growing number of clinical trials evaluating its pain-reducing efficacy in diverse chronic pain conditions [48].

MECHANISMS OF ECS ACTION

Cannabinoid binding and activation of CB1/CB2 receptors produce many pharmacologic effects resulting from ECS modulation of other neurotransmitter systems [49].

Shared CB Mechanisms

The ECS facilitates rapid local response to pathologic states or disease. Increased intracellular calcium release from neuronal activation or cellular stress triggers membrane phospholipids to synthesize and immediately release anandamide or 2-AG, which binds and activates nearby CB receptors. This activation inhibits adenylyl cyclase activity, decreasing cyclic adenosine monophosphate (AMP) formation and protein kinase A activity, which in turn blocks Ca2+ influx through various calcium channels. CB receptor activation also stimulates inwardly rectifying potassium (K+) channels and the mitogen-activated protein kinase signaling cascades. Cellular uptake and enzymatic degradation rapidly clear the endocannabinoids [50].

The ECS alters CB1 or CB2 receptor expression during stress response, which is beneficial in some pathologic states (e.g., neuropathic pain, multiple sclerosis) because increased CB expression may curtail symptoms or disease progression and provide a protective role. Alteration in CB1 expression is maladaptive in other disease conditions, such as CB1 up-regulation in liver fibrosis and down-regulation in colorectal cancer [50; 51; 52].

CB1 Mechanisms

In CNS tissue, CB1 activation inhibits neuronal calcium channels and activates potassium channels, as described. Anandamide and 2-AG are synthesized and released from post-synaptic neuron terminals, travel "backwards" across the synaptic cleft to pre-synaptic neurons, and bind CB1 receptors on pre-synaptic terminals. This, in turn, inhibits release from excitatory and inhibitory synapses of serotonin, glutamate, acetylcholine, gamma-aminobutyric acid (GABA), noradrenaline, dopamine, D-aspartate, and cholecystokinin. This process of post-synaptic release, backwards diffusion across the synaptic cleft, and pre-synaptic CB1 binding is termed "retrograde signaling" [36; 53; 54].

CB2 Mechanisms

As noted, CB2 receptor expression is highest in immune cells. CB2 activation mediates immunosuppressive effects, including inhibition of proinflammatory cytokine production and cytokine and chemokine release, and blockade of neutrophil and macrophage migration [36; 53; 54].

ECS and Pain Pathways

Pain is the most frequent condition for which medical cannabis is used, and the antinociceptive (analgesic) actions of cannabinoids are distinct from mechanisms that mediate psychoactive effects [10; 15]. For instance, THC enhances analgesia produced by kappa opioid receptor agonist drugs, and administration of a kappa opioid receptor antagonist blocks this analgesic effect but has no effect on the psychoactive effects of THC. Cannabinoids interact with opioid, serotonin, and *N*-methyl-d-aspartate (NMDA) receptors, all of which are highly relevant in pain modulation [37].

The efficacy of cannabinoids in the management of chronic neuropathic pain is partially explained by ECS modulation of the descending supraspinal inhibitory pathway, an important pain pathway functionally compromised in patients with chronic pain. Via periaqueductal grey and rostral ventromedial medulla inputs, cannabinoid activation of CB1 and CB2 receptors stimulates the endogenous noradrenergic pathway, which activates peripheral adrenoreceptors to induce antinociception. Other mechanisms of cannabinoid analgesia include functional CB2 receptor expression in dorsal root ganglion sensory neurons, the spinal cord, and brain regions highly relevant to nociceptive integration and modulation [37; 55].

Serious gastrointestinal and cardiovascular adverse effects are associated with nonsteroidal anti-inflammatory drugs (NSAIDs), and their use is now recommended at the lowest effective dose over the shortest duration possible [56; 57; 58]. In theory, cannabis may have NSAID dose-sparing effects.

Cannabinoids and cyclo-oxygenase-2 (COX-2) have independent but interacting roles in pain. During inflammatory pain, prostanoids are produced, potentiating bradykinin to sensitize pain signal-transmitting C-fibers. COX-2 metabolizes anandamide and 2-AG to prostanoid compounds that potentiate this pain-inducing cascade, and COX-2 oxidizes 2-AG into the pro-nociceptive metabolic product prostaglandin E2 (PGE2)-G. Thus, inflammatory states with COX-2 up-regulation can nullify the antinociceptive effects of endogenous cannabinoids and produce pro-nociceptive byproducts from their metabolism. COX-2 inhibitors block this conversion, an effect shown in peripheral pain where anandamide release is the dominant analgesic mechanism, and in stress-induced CNS pain where 2-AG release is the dominant analgesic. Low-dose COX-2 inhibitors do not block COX-2 but block the conversion of 2-AG into pro-nociceptive PGE2-G. Acetaminophen prolongs the analgesic action of 2-AG by inhibiting its enzymatic degradation by FAAH [55]. These findings indicate that co-ingesting cannabinoids and COX-2 inhibitors synergistically inhibits prostaglandin and enhances endocannabinoid activity to produce greater analgesia than monotherapy with either agent [59]. Also, tolerance is a main unwanted development with all analgesic drugs, including cannabinoids, and COX-2 inhibition may prolong cannabinoid analgesia [60].

CANNABINOID PHARMACOLOGY

Cannabinoids are the molecular constituents of botanical cannabis (also termed phytocannabinoids) or pharmaceutical preparations that possess ECS activity.

BOTANICAL CANNABIS COMPOSITION

Cannabis possesses at least 489 distinct compounds from 18 different chemical classes that include terpenoids, flavonoids, phytosterols, and at least 100 cannabinoids. This does not mean there are 100 different cannabinoid effects or interactions; the cannabinoids fall into 10 groups of closely related cannabinoids, and most are not believed to contribute to cannabis's effects at their naturally occurring concentrations in the plant. THC is the primary psychoactive ingredient, and depending on the particular plant, THC or cannabidiol (CBD) is the most abundant cannabinoid. The relative concentration of THC, CBD, and other cannabinoids in a given plant is influenced by cannabis strain, soil and climate conditions, and cultivation techniques [8; 61].

Pyrolysis transforms hundreds of plant cannabinoid compounds into additional compounds. More than 2,000 compounds may be produced through pyrolysis of cannabis, many of which remain to be studied. As such, smoked cannabis produces many compounds not observed with vaporized or ingested cannabis [14; 62; 63]. Phytocannabinoids are discussed in detail later in this course.

Terpenoids

Terpenoids vary widely among *Cannabis* varieties, accounting for differences in fragrance among different strains and possibly contributing to the distinctive smoking qualities and character of the "high" from smoked cannabis. Preclinical studies suggest a broad spectrum of activity with terpenoids, including anti-oxidant, antianxiety, antibacterial, antineoplastic, and antimalarial action; however, these data await confirmation in clinical trials [64; 65]. Analgesic and anti-inflammatory activity have been found in several cannabis terpenoids [66]. Myrcene is an analgesic that inhibits inflammation via PGE2 activity. Naloxone blocks this activity, suggesting an opioid-mediated mechanism [67]. β-caryophyllene produces anti-inflammation via PGE1 inhibition comparable to phenylbutazone and also acts simultaneously as a gastric cytoprotective. It possesses selective CB2 agonist activity, and additional investigation has shown increasing promise with potentially broad clinical application [68]. Other possibly therapeutic terpenoids include the PGE1 inhibitor α-pinene and the local anesthetic linalool [65; 69]. One study examined six common terpenoids, alone and in combination with cannabinoid receptor agonists, on CB1 and CB2 signaling in vitro [70]. The terpenoids were tested both individually and in combination for periods of up to 30 minutes. None of the six terpenoids tested directly activated CB1 or CB2 or modulated the signaling of THC [70]. A study that included five common terpenoids from *Cannabis* also found that none had direct interactions with CB1 or CB2 [71].

Flavonoids

Cannabis flavonoids are natural plant constituents also found in whole cannabis extracts. Beneficial activities from flavonoids include inhibition of TNF-α by apigenin, a potentially therapeutic mechanism in multiple sclerosis and rheumatoid arthritis; and PGE2 inhibition by cannflavin A, an action 30 times greater than PGE2 inhibition by aspirin [72]. One study evaluated the neuroprotective and anti-aggregative properties of cannflavin A and found that it demonstrated a neuroprotective role against the amyloid β-mediated neurotoxicity associated with Alzheimer disease [73].

Phytosterols

A number of phytosterols are present in cannabis, with specific effects associated with each. For example, the cannabis phytosterol β-sitosterol was found to reduce topical inflammation by 65% and chronic edema by 41% in skin models [74]. Cannabis root contains significant amounts of β-sitosterol and other sterols that can be extracted by various methods [75]. Extracts of cannabis root have been used to treat pain and inflammation for millennia by various cultures, including the Romans as described by Pliny the Elder.

PHARMACEUTICAL CANNABINOID PREPARATIONS

Following identification of THC as the primary active constituent in cannabis, investigative focus primarily involved the therapeutic potential of isolated THC. Although efficacy was found across many pathologic conditions, the prominent psychotropic effects of THC limited its clinical appeal. Discovery of the ECS and characterization of additional phytocannabinoids prompted research evaluation of the therapeutic potential of other phytocannabinoids lacking the psychotropic effects of THC. Investigation of CBD, cannabigerol, Δ9-tetrahydrocannabivarin, and cannabidivarin led to promising results in preclinical models of CNS disease. This research also revealed the basis for expanded receptor targeting beyond CB receptors with these agents and the suggestion of clinical utility in epilepsy, neurodegenerative diseases, affective disorders, and central modulation of feeding and appetitive behavior [76]. These findings have influenced the direction of modern cannabinoid drug development and evaluation. Many novel cannabinoid therapeutics are in early-stage safety and efficacy evaluation, and the following cannabinoids are in current clinical or advanced-phase investigative use.

Dronabinol

Dronabinol (branded as Marinol) is an isomer of THC, and across a wide range of oral doses, it is shown to be chemically identical to plant-derived THC [37]. Dronabinol was initially approved by the U.S. Food and Drug Administration (FDA) in 1985 for the treatment of chemotherapy-induced nausea and vomiting in patients lacking adequate response to existing antiemetics, and then in 1992 for anorexia and cachexia in patients with AIDS. Dronabinol is a Schedule III substance and is available in 2.5–10 mg oral capsules and 5 mg/mL oral solution [77].

Nabilone

Nabilone (Cesamet) is a Schedule II THC analog that is chemically similar but not identical to THC [37]. Approved by the FDA in 1985 for the treatment of chemotherapy-induced refractory nausea and vomiting and used off-label for analgesia, it is considered more potent than synthetic THC (e.g., dronabinol) [78]. It is administered (1 mg oral capsule) in doses of 1–2 mg twice daily for adults and 0.5–1 mg twice daily for pediatric patients [77].

Nabiximols

Nabiximols (Sativex) is a botanically derived cannabis extract with a defined 1:1 ratio of THC to CBD (27 mg/mL THC + 25 mg/mL CBD) delivered as a metered buccal spray. This drug has regulatory approval for select pain indications in 20 countries (including Canada) and is currently undergoing advanced phase III trials in the United States for treatment of cancer pain refractory to optimal opioid therapy [77; 79].

Cannador

Cannador is an orally administered cannabis extract containing a 2:1 ratio of THC to CBD. It is under investigation in Europe by the Institute for Clinical Research for the treatment of anorexia/cachexia in patients with cancer [80].

Pharmaceutical-Grade Smoked Cannabis

Smoked cannabis here applies to the medicinal cannabis produced in Canada and the Netherlands, because the exceptional quality, purity, and consistency controls are in line with pharmaceutical-level standards. In both countries, cannabis for medical or research use is grown by a single contractor, licensed by the government, under exceptionally strict, controlled, and documented conditions. From "seed to smoke," the seedlings are grown, packaged, and distributed via a centralized supply chain.

In the Netherlands, cannabis with the following THC and CBD concentrations are available [81]:

- 22%, 14%, or 13.5% THC with <1% CBD
- 6.3% THC/8% CBD
- <1% THC/9% CBD

In Canada, cannabis is available in potencies of [82]:

- 22% THC/<1% CBD
- 17% THC/<1% CBD
- 15% THC/5% CBD
- 12.5% THC/<0.5% CBD
- 9% THC/9.5% CBD
- 4% THC/10% CBD
- 0.7% THC/13% CBD

The cannabis used by the CMCR is of comparable pharmaceutical quality to the medical cannabis in the Netherlands and Canada [26]. In contrast, legal medicinal cannabis purchased from dispensaries in the United States lacks government-controlled standardization of cultivation, potency, and purity [83]. In the United States, cannabis grown for recreational or medical use has been bred to increase THC effects by increasingly reducing the CBD concentration. This also increases the side effect potential, and medical cannabis users may want to avoid this by seeking strains bred for higher CBD concentration [84].

PHYTOCANNABINOIDS

In contrast to pharmaceuticals that contain a single cannabinoid or a combination of two cannabinoids, the effects of inhaled cannabis are the result of pharmacologic activity from multiple agents. The psychoactive effects are largely the result of THC activity at the CB1 receptor. Therapeutic effects are influenced by THC and also by additional cannabinoids lacking psychoactive properties [8].

Δ-9-Tetrahydrocannabinol (THC)

THC is present in the living *Cannabis* plant as a mixture of monocarboxylic acids, and heating to greater than 120°C decarboxylates THC to promote biologic activity. THC decomposes from exposure to air, heat, or light, and oxidizes to cannabinol when exposed to acid [62; 63]. THC binds to CB1 and CB2 receptors as a partial agonist, with preferential binding at CB1. The mechanism of action, transmitter system interactivity, and demonstrated and theoretical therapeutic utility of THC are complex and vast, and the following summary is limited to the area of pain.

Among natural cannabinoids, THC possesses the greatest psychoactive potency and also exhibits the greatest analgesic activity. Epidural (i.e., intrathecal, intraventricular) administration of THC produces antinociception similar in magnitude to that of opioid analgesics [85].

Analgesic mechanisms of THC include interaction with serotonergic 5-hydroxytryptamine (5-HT) systems. THC inhibits 5-HT release from platelet cells, increases cerebral production of 5-HT, and decreases synaptosomal uptake. These effects involve multiple trigeminovascular system mechanisms associated with migraine headache. Dopaminergic inhibition by THC may also contribute to analgesic benefits [31; 86].

The glutamatergic system is foundational in chronic neuropathic pain and is causal in the development of secondary and tertiary hyperalgesia, via NMDA mechanisms, that characterize conditions such as migraine and fibromyalgia [87]. Cannabinoids inhibit pre-synaptic glutamate release, and THC reduces NMDA response by 30% to 40%. THC is also neuroprotective through antioxidant activity [88]. THC inhibits calcitonin gene-related peptide to reduce hyperalgesia, and preclinical studies show that THC blocks capsaicin-induced hyperalgesia at sub-psychoactive doses [89; 90].

THC stimulates beta-endorphin production, and this important opioid system interaction partially accounts for the repeated findings of the opioid sparing effects with cannabis in clinical trials and preventing development of opioid tolerance and withdrawal and the reinstatement of analgesia when a prior opioid dosage has worn off in other studies [91; 92].

THC also produces extensive anti-inflammatory activity through mechanisms that include inhibition of PGE2 synthesis, suppression of platelet aggregation, and stimulation of lipoxygenase. Studies have confirmed that THC produces 20 times the anti-inflammatory potency of aspirin and twice the potency of hydrocortisone, but unlike NSAIDs, it has not demonstrated COX inhibition [31; 93].

11-Hydroxy-THC

11-hydroxy-THC is the primary metabolic product of THC. It is four times more potent in producing psychoactive and immunosuppressive effects than the parent compound [62; 63].

Δ 8-THC

Δ8-THC is a Δ9-THC isomer found in smaller amounts in the cannabis plant and has activity as a partial CB1 and CB2 agonist. In vitro assays have shown comparable efficacy and potency with Δ9-THC, and preliminary clinical results suggest greater antiemetic potency with Δ8-THC compared with Δ9-THC [94; 95]. Δ8-THC is psychoactive, but the effect is very weak and substantially overshadowed by THC due to its low concentration [8].

In 2022, the FDA issued a warning letter and consumer update regarding products containing Δ8-THC [222]. These products contain concentrated amounts of Δ8-THC, typically manufactured from CBD. At the levels found in these products, the isomer induces significant psychoactive effects, and adverse effects have been reported, including hallucinations, vomiting, tremor, anxiety, dizziness, confusion, and loss of consciousness [222].

Cannabidiol

CBD has shown exceptional therapeutic promise as a single molecular entity. It is already in clinical use as a combination product with THC and in certain cannabis strains developed to overexpress CBD.

CBD produces pharmacologic actions different from, and often the opposite of, those of THC, and an increasing number of publications suggest broad therapeutic potential [96]. CBD is non-psychoactive but modulates ion channel, receptor, and enzyme targets. Preclinical studies suggest beneficial anti-inflammatory, analgesic, antiemetic, antipsychotic, anti-ischemic, anxiolytic, and antiepileptiform effects; human studies suggest anxiolytic efficacy [96; 97; 98]. CB2 receptor activity accounts for some anti-inflammatory and antinociceptive effects. CBD does not affect memory and probably curtails negative THC side effects by CB1 inverse agonist activity. The anxiolytic effects of CBD probably result from 5HT1-A receptor agonist activity [37].

Other mechanisms of therapeutic activity have been found. The neuroprotective properties of CBD are produced by inhibition of glutamate neurotoxicity and by antioxidant activity that surpasses ascorbic acid (vitamin C) and tocopherol (vitamin E) [88]. CBD modulates endocannabinoid activity as a TRPV1 agonist and an FAAH inhibitor, and through inhibition of THC first pass hepatic metabolism into the more highly psychoactive metabolite 11-hydroxy-THC, which prolongs THC half-life and reduces the unwanted THC side effects of intoxication, panic, anxiety, and tachycardia [99].

CBD inhibits tumor necrosis factor-alpha (TNF-α) in an animal model of rheumatoid arthritis and produces anti-inflammation and analgesia unrelated to COX-1 or COX-2 inhibition that involves promotion of adenosine receptor A2A signaling through adenosine transporter inhibition [31; 100]. Many effects of CBD follow a bell-shaped dose-response curve, suggesting that dose is a key factor in CBD pharmacology [97].

Outside of the United States, CBD is available in equal ratio to THC in the oromucosal spray nabiximols. In Canada and the Netherlands, some cannabis strains available for medicinal use have been bred to overexpress CBD, for a 1:1 ratio of CBD to THC. Pure (>99%) isolated CBD crystals, oils, waxes, and other extracts are available from many dispensaries.

In 2018, the FDA approved the first drug that contains purified CBD—a CBD oral solution for the treatment of seizures associated with Lennox-Gastuat syndrome and Dravet syndrome in patients 2 years of age and older [101].

Cannabinol

Cannabinol is produced by THC oxidation and is most often found in aged cannabis products. Cannabinol shares some characteristics with CBD, such as anti-convulsant and anti-inflammatory activity. Adding cannabinol to THC does not significantly increase THC effect. It is a weak CB1 and CB2 partial agonist with approximately 10% of the activity of THC and appears to possess immunosuppressive properties. Potential therapeutic applications of cannabinol include diseases characterized by cannabinoid receptor up-regulation [66; 97; 102].

Cannabigerol

Cannabigerol possesses a broad mechanistic range, with activity as a partial CB1 and CB2 receptor agonist, a potent TRPM8 antagonist, an agonist at TRPV1and TRPA1, and also as an anandamide reuptake inhibitor in the low micromolar range. Other mechanisms of cannabigerol include 5-HT1A receptor antagonism and α2-adrenoceptor agonism [97; 102]. Cannabigerol possesses anti-inflammatory and analgesic properties and also demonstrates antiproliferative and antibacterial activity [97].

Tetrahydrocannabivarin

Tetrahydrocannabivarin is a CB1 receptor antagonist and CB2 receptor partial agonist. This effect is dose-dependent, as it shows THC antagonist activity at low doses while higher doses act as a CB1 agonist. Tetrahydrocannabivarin has shown anticonvulsant properties in in vitro and in vivo studies [103; 104]. Other potential benefits of tetrahydrocannabivarin include its increase of central inhibitory neurotransmission, giving it therapeutic potential in epilepsy, and CB1 antagonism suggesting clinical benefit by decreasing food intake [97].

Cannabichromene

Cannabichromene, together with THC, is a major cannabinoid constituent in freshly harvested cannabis. It has activity as a potent TRPA1 agonist and weak anandamide reuptake inhibitor, and it is shown to exert anti-inflammatory, antimicrobial and modest analgesic activity. In preclinical animal studies, cannabichromene showed greater propensity than THC in producing adverse events, including hypothermia, sedation, and hypoactivity [97].

PHARMACOKINETICS

Cannabis is inhaled or orally ingested, with substantial differences between routes in the time course of absorption, distribution, and duration of action that explain the overwhelming preference of medical users for inhaled over orally ingested cannabis products [53]. In one study, more than 4,000 Californian medical patients expressed a preference for inhaling their medication, stating the therapeutic effects from oral dronabinol or nabilone were more difficult to achieve and more likely to be unpleasant or excessively prolonged [105]. In contrast, inhaling cannabis provides more rapid onset of symptom relief and rapid feedback informing the patient whether titration with additional dose is needed or not [62; 106].

Absorption and Distribution

The rate of drug absorption is determined by the route of administration and drug formulation. Inhalation is the primary route of cannabis administration and provides rapid and efficient drug delivery from the lungs to the brain [62].

Smoked Cannabis

With smoking, the onset of effect occurs within seconds to minutes. Maximal effect is experienced after 30 minutes, and the duration of effect is 2 to 3 hours [53]. Peak plasma THC occurs within 10 minutes and decreases to roughly 60% of peak by 15 minutes and to 20% of peak by 30 minutes. This rapid onset and predictable decay allows for effective dose titration not possible with oral cannabinoids [83]. The THC dose absorbed systemically is 25% to 27% of the total available THC content in a marijuana cigarette ("joint") [62; 107].

Vaporized Cannabis

A study comparing smoked and vaporized administration found higher serum THC at 30 and 60 minutes post-inhalation with vaporization and comparable serum THC levels over the remaining six-hour period [108]. Vaporization was preferred by 80% of subjects, and as with smoking, vaporization was highly conducive to self-titration. The amount of THC delivery is influenced by the amount and type of cannabis, vaporizing temperature, duration of vaporization, and the balloon volume [109; 110].

Oral Ingestion

The CNS and physiologic effects with oral ingestion are substantially delayed relative to inhalation, including slower onset of action, lower peak plasma levels, and longer duration of effect. With pharmaceutical cannabinoids such as dronabinol, 10% to 20% of ingested THC enters systemic circulation due to extensive first-pass metabolism. In healthy volunteers, a single 2.5-mg dose of dronabinol produces mean peak plasma THC at two hours, with a range of 30 minutes to four hours; these absorption and distribution kinetics are similar following a single 10-mg dose of dronabinol [111].

Plant cannabis can be mixed into brownies, cookies, or tea prepared from the flowering tops, but all result in unreliable absorption. In one study, oral ingestion of 20 mg THC in chocolate cookies resulted in only 4% to 12% of THC entering systemic absorption and peak plasma THC at one to two hours in most subjects and six hours in others, with some subjects showing multiple plasma peaks [62]. The bioavailability of THC from tea made of plant cannabis is lower than with smoking due to the poor water solubility of THC and the effect of hepatic first-pass metabolism [14].

Distribution

THC distribution is time-dependent and begins rapidly after absorption. In plasma, THC is 95% to 99% plasma protein bound, primarily lipoproteins. The tissue distribution of lipophilic THC and its metabolites mostly involves uptake in fatty tissues and highly perfused organs such as the brain, heart, lung, and liver [53; 62]. Whether THC accumulates in the brain with long-term use is unknown, due to limits in THC access and accumulation imposed by the blood-brain barrier [112].

Metabolism

Most cannabinoid metabolism occurs in the liver, with different metabolic byproducts predominating by route of administration. THC metabolism is complex and involves allylic oxidation, epoxidation, decarboxylation, and conjugation. THC is oxidized by the cytochrome P450 (CYP450) oxidases 2C9, 2C19, and 3A4 to produce the active metabolite 11-hydroxy THC and the inactive metabolite 11-nor-9-carboxy THC [113]. The 11-hydroxy THC plasma level parallels observable drug action [62]. Relative to inhalation, first-pass hepatic metabolism with oral ingestion yields a greater proportion of 11-hydroxy THC [53].

Elimination

Body fat is the major long-term storage site of THC and its biometabolites. Elimination occurs over several days due to the slow rediffusion of THC from body fat and other tissues. Roughly 20% to 35% of THC is eliminated in urine and 65% to 80% in feces, and by five days, 80% to 90% of THC is eliminated, although THC from a single dose can be detected in plasma up to 13 days later in chronic smokers as a result of extensive storage and release from body fat [53; 114].

Adverse Drug-Drug Interactions

Most patients in the RCTs discussed in this course were maintained on their pre-study medications for neuropathic pain, cancer pain, fibromyalgia, or multiple sclerosis. In these and other RCTs, patients smoked or ingested cannabis while taking their prescribed opioids, NSAIDs, muscle relaxants, ketamine, anticonvulsants, antidepressants, and benzodiazepines. Cannabis use with these other agents was well tolerated, and observed side effects did not differ from those expected with cannabis [14].

In theory, ingesting cannabis with drugs that alter its metabolic pathway should increase the risk of side effect enhancement or efficacy failure, but adverse drug-drug interactions of clinical relevance have not been reported to date. Cannabis should be used with caution by patients also using sedating substances such as alcohol or benzodiazepines [53].

Tolerance

Tolerance is defined as tissue adaptation resulting from repeated drug exposure, such that one or more drug effects diminish over time. Cannabis tolerance primarily results from pharmacodynamic mechanisms, including changes in CB1 signaling ability due to receptor desensitization and down-regulation. THC tolerance varies across different brain regions, possibly explaining why tolerance develops to some cannabis effects but not to others [115]. Tolerance to most THC effects develops after a few doses and then disappears rapidly following cessation, and pharmacodynamic tolerance can be minimized by combining a low dose of cannabinoid with one or more additional therapeutic drugs [116].

SIDE EFFECTS AND SAFETY

Information on medical cannabis safety and side effects should ideally come from RCTs that control for confounding factors that may otherwise account for the results. Such studies are increasingly being published, but similar to other drug efficacy trials, safety information is available with short-term (less than three months) use while long-term safety data remains sparse. In contrast to studies with medicinal users, many studies of long-term heavy recreational users have been published. Generalizing safety outcomes from chronic recreational users to medicinal users is cautioned against because of numerous confounding factors, including differences in age of first regular use; duration, quantity, and THC content of cannabis use; concurrent alcohol or other drug use; drug delivery approaches; and past or current psychiatric, neurologic, and comorbid medical histories [117; 118; 119]. Raphael Mechoulam, who in 1964 co-discovered THC, concluded that most cannabis safety data from "street users" are "useless" (his words) for extrapolation to medicinal cannabis safety, based on the before-mentioned factors and the widely variable THC and unknown CBD content of illicitly obtained cannabis in contrast to cannabis now cultivated under tightly controlled environmental conditions to ensure reliability [120; 121]. In the following sections, the available evidence on medical cannabis and pharmaceutical cannabinoids is presented.

RISK/BENEFIT CONSIDERATIONS

Importantly, the potential acute and long-term adverse effects with medical cannabis should be weighed against the known side effect profiles of standard therapeutic agents for the same indication [83]. For example, in standard therapies for chronic pain or spasticity, opioids often produce sedation, nausea, constipation, physiologic dependence, and with abrupt cessation of long-term use, a more severe withdrawal syndrome than cannabis withdrawal. Tricyclic antidepressants and antiepileptic drugs are frequently prescribed for chronic neuropathic pain and may produce sedation, constipation, dizziness, palpitations, visual disturbance, urinary retention, and neuromuscular effects. Antispasmodic drugs may produce sedation (e.g., baclofen), hypotension (e.g., tizanidine), and potentially serious interactions with antibiotics (as with tizanidine and ciprofloxacin). Benzodiazepines prescribed for spasticity may produce sedation, psychomotor incoordination, memory impairment, paradoxical reactions, dependence, and with daily long-term use, a severe protracted withdrawal syndrome. Opioids and benzodiazepines are also drugs with potential for abuse, addiction, diversion, and fatal overdose exceeding cannabis. This comparison helps put consideration of the relative benefits and risks of medical cannabis in the proper context [83].

As with any drug therapy, important considerations include the dose-response relationship and margin of safety that separates beneficial dose from dosage producing adverse effects [2]. Safety concerns can be addressed, as with any drug, by appropriate patient screening and monitoring, adherence to known contraindications, and administration with alternative delivery systems (as in patients with lung disease). In many (non-cannabis) contexts, clinical medicine involves balancing risk and benefit even when limited evidence is available to base a decision, and the needs and wishes of patients should be considered while the merits of medical cannabis use are debated [15].

Cannabinoid-drug interactions should be considered in all patients. CBD and possibly THC are known to increase the levels of direct-acting oral anticoagulants and clopidogrel. In patients using cannabis or products containing CBD or THC, other agents should be considered [224]. THC and CBD also inhibit metabolism of warfarin, which can lead to elevated INRs. There is also some evidence that cannabis or cannabinoid use can effect postoperative outcomes. As such, the American Society of Regional Anesthesia and Pain Medicine (ASRA) recommends universal screening for cannabinoids prior to surgery, including type of cannabis or cannabinoid product, time of last consumption, route of administration, amount, and frequency of use [224].

PHARMACOLOGIC MANAGEMENT OF CANNABIS SIDE EFFECTS	
Symptom	**Therapeutic Agent**
Palpitations and tachycardia	Propranolol
Arrhythmia, atrial fibrillation	Flecainide, propafenone, digoxin
Acute psychotic state	Olanzapine, haloperidol
Acute intoxication	Propranolol
Acute anxious psychotic symptoms from very high-dose THC	Cannabidiol
Acute panic anxiety state	Lorazepam, alprazolam
Acute manic and depressive syndromes during intoxication	Benzodiazepines, antipsychotics
Cognitive impairment with repeated use	COX-2 inhibitors[a]
[a]Based on preclinical studies of primates.	
Source: [127; 128]	*Table 2*

Further, the ASRA recommends delaying or postponing elective surgery in patients who are acutely intoxicated or who have recently smoked cannabis.

DATA FROM PHARMACEUTICAL CANNABINOID TRIALS

Cannabinoid safety and side effect data from 23 RCTs and 8 observational studies involving 1,932 participants with medical conditions such as cancer and multiple sclerosis were reviewed [117]. The cannabinoids included dronabinol and nabiximols spray. In the RCTs, median cannabinoid exposure was two weeks (range: 8 hours to 12 months). Serious adverse events occurred in 164 cannabinoid subjects and 60 control subjects; the most frequent by category were respiratory (16.5%), gastrointestinal (16.5%), and nervous system disorders (15.2%) with cannabinoids, and nervous system disorders (30%) with placebo. The difference in incidence between cannabinoid and placebo subjects was not statistically significant. Non-serious adverse events were significantly more prevalent with cannabinoids, with the most common being blurred vision, dry mouth, weakness, dizziness, somnolence, sedation, confusion, hypotension, and altered mood [117]. Data from two recent high-quality systematic reviews found sufficient evidence that cannabinoids (e.g., nabiximols, nabilone, dronabinol) may be effective for reducing the symptoms of patient-reported pain and spasticity in multiple sclerosis [122; 123]. A systematic review conducted by the American Academy of Neurology found that oral cannabis extract is effective for symptoms of spasticity in patients with multiple sclerosis and that nabiximols and THC are probably effective for reducing patient-centered measures [124].

DATA FROM MEDICINAL CANNABIS TRIALS

Results from RCTs of smoked cannabis found that side effects were generally dose-related, mild-to-moderate in severity, time-limited, and less common in experienced cannabis users. Most frequent were dizziness or lightheadedness (30% to 60% of subjects), dry mouth (10% to 25%), fatigue (5% to 40%), muscle weakness (10% to 25%), myalgia (25%), and palpitations (20%). Cough and throat irritation occurred initially in a few participants. Euphoria was reported in some but not all subjects, with the low incidence attributed to plasma THC concentrations less than 25% of the levels generally found with recreational cannabis use. Infrequently, tachycardia and postural hypotension were noted, a potential concern in patients with cardiovascular disease. Tachycardia was a frequent acute physiologic effect, with it and other acute cardiovascular effects rapidly resolving due to the brief period of THC occupancy and then distribution out of the circulatory system [14].

A dose-effect relationship was found, with higher rates of sedation, ataxia, and loss of balance following higher dose levels [125; 126]. Tolerance to cardiovascular, autonomic, and other subjective and cognitive side effects developed rapidly over the initial 2 to 12 days of therapy [83]. As with other therapeutics, large inter-individual differences in side effects were observed, and severely ill patients, elderly persons, and patients taking multiple concurrent medications may be especially prone [14]. Anxiety or psychotic symptoms were uncommon, dose-related, occurred primarily during acute administration of high doses, and in most cases could be avoided by dose titration [54]. Successful resolution or management of cannabis side effects has been described with several agents (***Table 2***) [127].

AREAS OF SAFETY CONCERN

Contaminants in the Cannabis Plant

Cannabis may be contaminated by a variety of organisms, such as *Aspergillus* fungus and bacteria, that can result in fulminant pneumonia, especially in immunocompromised persons. Nonbiologic contaminants can include heavy metals such as aluminum and cadmium from the soil, with cadmium readily absorbed into the plant at high concentrations. Organophosphate pesticides are found less often in cannabis grown outdoors versus indoor cultivation [129]. Concerns over inorganic and biologic contaminant ingestion prompted Health Canada and the OMC to carefully control all aspects of cultivation, test the product for the presence of mold spores and 28 different metals including heavy metals, and pre-emptively irradiate all cannabis products before distribution to medical or research users [27; 82]. This is not currently done to most cannabis available in the United States.

Pulmonary Function

Physician and patient concerns over pulmonary harm from cannabis smoking have been based on the known hazards from smoking tobacco, findings of carcinogenic compounds in cannabis smoke, and earlier epidemiologic studies associating long-term cannabis use with respiratory dysfunction [130]. This has contributed to reluctance over medical smoked cannabis use.

Although many carcinogens and tumor promoters are common to tobacco and cannabis smoke, differences in the active constituents result in different biologic outcomes. Molecules in tobacco smoke enhance carcinogenic pathways through several mechanisms, including circumvention of normal cellular checkpoint protective mechanisms; activation of respiratory epithelial cell nicotine receptors; promotion of tumor angiogenesis; stimulation of enzymes that convert polycyclic aromatic hydrocarbons found in smoke into carcinogens; and prevention of apoptotic cascades (cell death) in cells accumulating sufficient genetic damage. In contrast, molecules in cannabis smoke inhibit carcinogenic pathways through down-regulation of immunologically generated free radical production (the innate response to inhaled smoke and particulate); THC blockade of enzymatic conversion of smoke constituents into carcinogens; the absence of cannabinoid receptors in respiratory epithelial cells (which maintains DNA damage checkpoint mechanism integrity with prolonged cannabis smoke exposure); and the anti-angiogenic, tumor-retardant, and anti-inflammatory activity of many cannabinoid smoke constituents [131; 132; 133].

These factors appear in the results of a 20-year longitudinal study of pulmonary health in 5,115 participants who smoked cannabis [134]. The authors stated that pulmonary risks from cannabis smoking had been overstated and found that, unlike tobacco smoking, cannabis smoking had no effect on measures of pulmonary function. Medicinal use of smoked cannabis was also found to be very unlikely to produce adverse effects on pulmonary function [134]. In 878 Canadians 40 years of age and older, history of tobacco smoking or tobacco and marijuana smoking, but not marijuana-only smoking, significantly elevated the risk of respiratory problems or chronic obstructive pulmonary disease (COPD) relative to non-smokers [135]. A 2022 study comparing 56 cannabis smokers and 33 tobacco-only smokers, the cannabis smokers showed higher rates of emphysema and airway inflammation than nonsmokers or tobacco-only smokers [223].

However, the researchers were careful to point out that high rates of concomitant tobacco smoking in the cannabis group made drawing firm conclusions difficult.

Vaporizing systems have been developed to further minimize pulmonary risks from smoked cannabis. These involve heating the plant material short of combustion and then inhaling the mist (instead of smoke). Vaporization may produce smaller quantities of the toxic smoking byproducts carbon monoxide, polycyclic aromatic hydrocarbons and tar, and compared with smoked cannabis, vaporization was found to significantly reduce carbon monoxide levels [108; 109]. One study evaluated the subjective and physiologic effects and expired carbon monoxide in frequent and occasional cannabis users following placebo, smoked, vaporized, and oral cannabis [136]. Participants' subjective ratings were significantly elevated compared with placebo after smoking and vaporization; only occasional smokers' ratings were significantly elevated compared with placebo following oral dosing. Smoking produced significantly increased expired carbon monoxide concentrations post-dose compared with vaporization [136].

Immunosuppression

Concern was raised in the 1990s over the potential negative effects of cannabinoids on immune function in immunosuppressed patients, particularly those with HIV. Data from several studies have alleviated these concerns. In HIV patients randomized to placebo, dronabinol, or smoked cannabis for 21 days, both cannabinoid groups failed to show increased viral load or reductions in protease inhibitor levels or CD4 or CD8 cell counts. Both cannabinoid groups showed statistically significant weight increases, and the smoked cannabis group showed significantly increased CD4 and CD8 counts [137]. Supportive data include a study of primates injected daily with THC before and after infection with simian immunodeficiency virus (SIV). Contrary to expectations, chronic cannabinoid exposure did not increase viral load or diminish immune function. Instead, the primates given THC showed significantly decreased rates of early mortality from SIV infection, associated with attenuation of plasma and cerebrospinal fluid viral load and retention of body mass [138]. Other conformational findings include a 10-year follow study of HIV patients, which found that regular cannabis smoking had no effect on viral load or CD4 and CD8 cell percentages [139]. An exception comes from preclinical trial results suggesting that increased CB2 activity may impose risks in immunocompromised patients with specific infection, such as *Legionella* [53].

Neurocognitive Impairment

There is abundant evidence from studies in adult subjects that smoking cannabis has an acute effect on motor coordination and impairs verbal and working memory for several hours after ingestion, an effect mitigated by several factors, including the degree of previous exposure to cannabis, the dose of THC, the ratio of THC to CBD, and genetic susceptibility [140]. These effects on cognition, mediated by THC, appear to resolve within hours to days after cessation of cannabis exposure.

The long-term effects of chronic cannabis use are more subtle and complex and involve multiple domains of cognitive function, as evidenced by psychologic testing and brain imaging studies. A growing body of evidence indicates that while significant neuropsychologic deficits may develop following chronic cannabis use, these deficits are largely reversible if chronic use did not commence until after one achieves adulthood (i.e., after full anatomic maturation of the brain). Early-onset (in adolescence) and long-term use of cannabis causes the greatest morphologic and functional impairments in the still-developing brain, and these deficits may not resolve completely after cessation of usage [140; 141].

Results from the 2012 Dunedin study provide the most definitive data on neurocognitive effects from cannabis use [142]. This prospective study followed 1,037 individuals from birth in 1972/1973, assessed their cannabis use at ages 18, 21, 26, 32, and 38 years. Neuropsychologic testing was administered at 13 years of age, before cannabis use was initiated, and at 38 years of age, after persistent cannabis use patterns were established. Family member informants provided corroborating input. Among adolescent-

onset, heavy cannabis users, there was an average decline in IQ of 8 points from 13 years of age to 38 years of age (impairment that was global and detectable across five domains of neuropsychologic functioning) and attention and memory problems observable by informants. Following cessation or infrequent use (median past-year use: 14 days) for one year, the IQ decline remained significant. In contrast, adult-onset heavy cannabis users did not exhibit IQ decline as a function of persistent cannabis use. The authors concluded that these findings suggest a neurotoxic effect of cannabis on the developing adolescent brain [142].

While cognitive function in long-term medical cannabis users has not been evaluated, a review of the published research on short- and long-term cognitive function in recreational users suggests that cognitive impairment is unlikely to persist beyond the acute intoxication state, even with high-THC cannabis, in late-onset users, short-term users, and occasional users [140].

Amotivational Syndrome

Amotivational syndrome is not a medical diagnosis but a term used to describe adolescents and young adults who lose interest in and drop out from school, work, socializing, and other goal-directed activities. Cannabis has been cited as the cause when its heavy use accompanies these symptoms, but evidence of causality is lacking [8; 119].

Schizophrenia and Psychoses

An acute psychotic reaction to cannabis has been described and is more likely to occur in young adults who are under stress and have a pre-existing vulnerability to psychoses or schizophrenia. An association has been found between cannabis use history and schizophrenia, but the causal direction of this link has not been established, with many studies suggesting causality showing instead a non-specific association between the most severe levels of cannabis use and a wide range of adverse psychosocial outcomes [119; 143]. Furthermore, cannabis use in the general population soared between 1949 and 1995, while the population rates of schizophrenia remained stable [144].

However, a subgroup of patients who are genetically vulnerable to cannabis-induced acute psychoses, and possibly cannabis-initiated schizophrenia, carry a functional polymorphism in the catechol-O-methyltransferase gene and a polymorphism in the brain-derived neurotrophic factor gene. Considering the potentially substantial risks, cannabis should be avoided in adolescents and adults with current, past, or family history of any psychotic disorder [53; 145].

Toxicity and Overdose

There are no cases in the literature of death due to toxicity following the maximum oral THC dose in dogs (up to 3,000 mg/kg THC) and monkeys (up to 9,000 mg/kg THC). In animals and humans, it is virtually impossible to induce fatal toxicity, and no human fatalities resulting from cannabis ingestion have been documented to date [37].

The side effect profile of medical cannabis is comparable to those produced by other medications tolerated by patients and approved for clinical use by the FDA [116; 146]. The rare acute complications resulting in emergency department presentation, such as panic attacks, psychosis, or convulsions, can be managed with conservative measures such as reassurance in a quiet environment and IV administration of benzodiazepines if needed [82; 147].

The greatest risk for toxicity and potential overdose is among children who may consume cannabis edibles, beverages, or candies inadvertently [148; 149]. A concern with toxic reactions is self-harm. In 2014, a young man (19 years of age) from Colorado died after consuming an edible marijuana product (a cookie). The decedent initially ate only a single serving (one-sixth of the cookie), as directed by the sales clerk. Each serving contained approximately 10 mg of THC. Approximately 30 to 60 minutes later, after not feeling any effects, the decedent consumed the remainder of the cookie. For the next two hours, the young man exhibited erratic speech and hostile behaviors. About 3.5 hours following initial ingestion, he jumped off a fourth floor balcony and died from trauma [150]. In adults, most toxic reactions are mild, but in children, overdose can result in significant respiratory depression [149]. Signs can

include somnolence, hallucinations, dyspnea, CNS depression, and even coma. Healthcare professionals should assess for availability of cannabis in the household if these signs present with no known explanation. If necessary, airway management and ventilation may be administered.

As "Gateway Drug"

The sensationalized 1980s theory of marijuana as the gateway to hard drug use lacks empirical support. While heavy adolescent use is associated with risk of other drug abuse, there is no good evidence of causality or directionality, and the large majority of cannabis users do not progress to "hard" drug use [19; 151]. Alcohol and nicotine use are more significant primers for hard drug use in many individuals [151]. Further research is necessary to clarify these points.

Cannabis Withdrawal Syndrome

Until recently, considerable doubt surrounded the possibility of a cannabis withdrawal syndrome; however, cannabis withdrawal syndrome has now been unequivocally demonstrated in heavy chronic recreational users [152]. With abrupt cessation, withdrawal symptoms emerge within one to two days, reach peak intensity after two to six days, and generally resolve within one to two weeks. Common symptoms include irritability or anger, nervousness, tension, restlessness, reduced appetite, insomnia and sleep difficulties, dysphoria, and craving. Less frequent symptoms are chills, stomach pain, shakiness, and sweating [153]. Cannabis withdrawal can resemble a low-grade opioid withdrawal but usually lacks the severe aches and pains, piloerection, diarrhea, sweating, stuffy nose, and muscle spasms common to opioid withdrawal [28; 119].

The severity of cannabis withdrawal, and whether it develops at all in strictly medical users, is unknown. With cessation of regular medical use, the pharmacokinetics and possibly pharmacodynamics of THC, such as slow elimination, may diminish withdrawal symptom manifestation into the subclinical level of severity [28].

Cannabis Addiction

Roughly 9%, or 1 out of 11, who use recreational marijuana will develop an addiction syndrome; the figure increases to 17%, or 1 out of 6, who begin use in their early teens [19; 154]. This compares with lifetime prevalence rates of 32% for nicotine, 23% for heroin, 17% for cocaine, and 15% for alcohol [19; 155; 156].

Addiction risk among medical cannabis users is unknown. Data on cannabis addiction and risk factors come primarily from recreational users who began during adolescence or early adulthood and used high-potency cannabis with great frequency and intensity in the absence of medical supervision. Whether these data apply to the typically older adult patient using smaller doses of medical marijuana for symptom control is not known [157].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Hartford Institute for Geriatric Nursing, little research on effective intervention for psychologic dependence on marijuana is available. Some guidance can be found in smoking cessation and self-help approaches.

(https://hign.org/consultgeri/resources/protocols/substance-misuse-and-alcohol-use-disorders. Last accessed November 11, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

The psychoactive effects and potential abuse liability of recreationally used cannabis are well known, but little is known of this potential with nabiximols spray (equal-ratio THC and CBD). A safety analysis using all published and unpublished nabiximols RCTs found that intoxication scores were low [155]. Euphoria was reported by only 2.2% of subjects, development of tolerance was not documented, abrupt cessation did not result in a withdrawal syndrome, and no cases of abuse or diversion were reported. An abuse liability study of nabiximols in experienced recreational cannabis smokers found some abuse potential at higher doses relative to placebo, but consistently lower abuse liability than equivalent doses of pure THC [155].

Although medical marijuana laws in some states have been anecdotally linked to increased recreational use among adolescents, a 2013 evaluation of the effects of these laws on adolescent marijuana use from 2003 through 2011 found that they had no measurable effect [158].

Cannabinoid Hyperemesis Syndrome

Cannabinoid hyperemesis syndrome (CHS) is characterized by severe cyclic nausea and vomiting in chronic (usually heavy) cannabis users [159]. It is a relatively rare adverse effect, but increasing case reports have been noted with the liberalization of cannabis in several states [160]. Individuals with CHS experience temporary relief of symptoms with hot baths or showers, and compulsive bathing is often an identifying feature (differentiating the condition from other causes of cyclic vomiting) [161]. Typically, patients begin with recurrent nausea and progress to intense, persistent vomiting with continued use of cannabis.

The underlying pathogenesis of CHS is unclear, although several theories have been presented. One theory is that the enteric emetic effects of cannabis (e.g., decreased gastrointestinal motility) may promote emesis by over-riding the antiemetic effects mediated by the CNS [161]. Symptoms resolve with cessation of cannabis use; relapse to use often results in a recurrence of the syndrome.

TREATMENT EFFICACY

Neurologists in the 1970s began identifying two distinct patient groups self-medicating with cannabis for symptom alleviation: wounded Vietnam War veterans with traumatic spinal injury and female patients with multiple sclerosis, migraine, or menstrual pain. Although these observations led to several small clinical trials supporting the claims of individual patients, regulatory hurdles in conducting clinical research resulted in relatively few efficacy studies [146]. Since 2000, there has been a significant increase in the quantity and quality of cannabis efficacy studies.

For some clinical conditions, most of the published research involves oral cannabinoids, and there are questions over the extent this efficacy can be extrapolated to cannabis. Some reports indicate that patients benefiting from oral cannabinoids are likely to benefit from smoked cannabis, but the reverse is not always true [154]. For example, inhaled cannabis trials for the management of nausea and vomiting are sparse. Although RCTs of dronabinol or nabilone predominate and have consistently shown efficacy, patients tend to prefer smoked over oral delivery due to the rapid alleviation of nausea and vomiting, ease of titration, and greater tolerability. Thus, for indications for which cannabis RCTs are few or absent, it seems reasonable to extrapolate non-cannabis cannabinoid efficacy to smoked cannabis.

CHRONIC PAIN

As noted, cannabis and other cannabinoids are seldom considered first-choice therapeutic options but are used instead in patients for whom standard therapies are ineffective or intolerable either as sole therapy or more typically as an add-on to the current regimen [2]. Cannabis has been safely co-administered with a wide range of other drug agents (as discussed) and acts synergistically with opioids to enhance analgesia and allow opioid dose reduction. Chronic pain treatment often requires multiple drug agents that target different pain mechanisms, and the novel mechanism and superior safety profile of cannabis versus opioids suggests that it can be a valuable addition to therapeutic options for chronic pain [162; 163].

Chronic pain is a highly prevalent, heterogeneous group of disorders that in many patients is refractory or only partially responsive to treatment [162]. Many cannabis analgesia studies use a benchmark of more than 30% reduction in pain intensity, because a 30% decrease in pain has been validated as the threshold necessary for meaningful improvements in quality of life [26]. The following studies on chronic pain are presented in greater detail because their results and the scientifically rigorous conditions under which they were conducted are now regarded as providing the most definitive evidence of efficacy [83].

Neuropathic Pain

More than 2 million Americans currently suffer chronic and debilitating neuropathic pain from trauma or disease affecting the peripheral or central nervous system. These conditions include diabetic neuropathy, nerve compression syndromes, postherpetic or trigeminal neuralgia, stroke, multiple sclerosis, and spinal cord injury. Neuropathic pain is comprised of a sensory component of allodynia (pain response to benign stimuli) and hyperalgesia (exaggerated pain to mild provocation), and an affective component of prominent anxiety or depression, diminished motivation, and changes in motor control. Neuropathic pain is difficult to treat, and while the sensory and affective components may respond to opioid therapy, this drug class often produces intolerable side effects or fails to provide meaningful pain reduction. Earlier trials suggested effective analgesia with cannabis, and priorities in finding therapeutic alternatives to high-potency opioids prompted investigation of cannabis efficacy in neuropathic pain [164; 165]. Finding even modest clinical benefit is important given the limited treatment options for these patients, and the RCTs uniformly found the number needed to treat to achieve 30% pain reduction was 3.5 for cannabis [166; 167]. In one study, use of nabiximols was found to be the most effective cannabinoid for multiple sclerosis-associated central pain [165]. Unless otherwise noted, the RCT methods in the following sections were double-blinded and placebo-controlled with inert, non-active cannabis and/or pills.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Institute for Health and Care Excellence recommends against starting *Cannabis sativa* extract to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so.

(https://www.nice.org.uk/guidance/cg173. Last accessed November 11, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

HIV-Associated Distal Sensory Polyneuropathy

In a five-day trial of 55 patients with HIV-associated distal sensory polyneuropathy, overall daily pain levels were reduced by 34% with active cannabis vs. 17% with placebo, and pain reduction of more than 30% was attained by 52% with active cannabis vs. 24% with placebo; both differences in pain reduction were statistically significant. Cannabis was well tolerated and no safety concerns were raised. Cannabis produced more side effects than placebo, the most common being sedation, anxiety, and dizziness, all rated as "mild" in severity [168].

Another study titrated 34 patients with HIV-associated distal sensory polyneuropathy to individualized effective and tolerated inhaled cannabis doses. Titration started with 4% THC or placebo, with downward or upward adjustment for problematic side effects or incomplete pain relief, respectively. In five study phases over seven weeks, >30% pain reduction was attained by 46% with cannabis vs. 18% with placebo (statistically significant). Side effects were more frequent with cannabis, the most common being sleepiness or sedation, fatigue, and difficulty concentrating. Aside from acute psychotic symptoms developing early in the only cannabis-naïve subject, all side effects were "mild" and no safety concerns emerged [169].

Both of these studies restricted enrollment to patients with refractory pain despite optimal pharmacologic management, and all patients remained on their pre-study analgesic therapies. Of note, the significant magnitude of pain reduction in HIV neuropathy with cannabis therapy represents an important medical finding, because this type of pain has been notoriously resistant to standard treatment approaches [54].

Neuropathic Pain of Heterogeneous Origin

A trial of 38 patients with complex regional pain syndrome (Type I), physical trauma to nerve bundles, spinal cord injury, multiple sclerosis, or diabetes smoked a single high- (7%), low- (3.5%), or 0% THC (placebo) cannabis cigarette in three six-hour sessions [170]. Previous cannabis exposure was required. Low- and high-THC cannabis produced

effective analgesia with comparability, suggesting a dose ceiling. Unpleasant side effects were more frequent with high-dose THC. Side effects were comparable between low-dose and placebo, and no subject terminated their involvement from side effects. Negative mood changes (e.g., sadness, anxiety, fearfulness) were not found. The authors stated the effects produced by cannabis were comparable to those observed with opioid analgesics, with pain relief resulting from equal alleviation of the affective and sensory component of pain but not resulting from a relaxing or tranquilizing effect [170].

Chronic Post-Traumatic or Postsurgical Neuropathic Pain

In an RCT with crossover, 23 subjects with chronic post-traumatic neuropathic pain smoked a single 25-mg dose of 0%, 2.5%, 6%, or 9.4% THC cannabis, three times daily over four 14-day periods alternating with 9-day washout [126]. The average daily pain intensity score was significantly lower with high-dose (9.4%) THC than with placebo. Intermediate potencies showed reduced but non-significant pain reduction vs. placebo. In addition, the 9.4% THC dose significantly improved ability to fall asleep and sleep quality compared with placebo. Side effects were more frequent with 9.4% THC cannabis and included headache, dry eyes, burning sensation in areas of neuropathic pain, dizziness, numbness, and cough. Most side effects were mild, and no serious or unexpected adverse events occurred. The authors concluded that single-inhalation 9.4% THC cannabis reduced pain intensity, improved sleep, and was well tolerated in these patients [126].

Vaporized Cannabis in Chronic Neuropathic Pain

In an RCT with crossover, patients with central or peripheral neuropathic pain resistant to conventional drug therapies received single-dose 3.53% THC, 1.29% THC, or 0% THC (placebo) cannabis [171]. Significant analgesic response was found with active but not placebo cannabis. Analgesia was equivalent with medium- vs. low-dose cannabis. Psychoactive effects were minimal and well tolerated, and neuropsychologic effects reversed within one to two hours. The authors state their findings of analgesic efficacy with low-dose cannabis in treatment-refractory neuropathic pain have large clinical value and that a negative impact on daily functioning is unlikely based on the observed side effects [171].

Experimental Neuropathic Pain

To examine the dose-by-time analgesic effect of cannabis, 19 healthy volunteers received capsaicin injection under the skin to simulate neuropathic pain and were administered in random sequence low-, medium-, and high-dose cannabis (2%, 4%, and 8% THC) or placebo cigarettes [172]. No effect on capsaicin-induced pain was found at any dose five minutes after smoking. At the 45-minute time point, there was a significant pain decrease with 4% THC, a significant pain increase with 8% THC, and no differences with 2% THC or placebo. A significant inverse relationship between pain perception and plasma THC was also found. The authors conclude a "therapeutic window" (or optimal dose) may exist for smoked cannabis with acute neuropathic pain, with low doses ineffective, medium doses efficacious, and higher doses pain-enhancing [172]. This biphasic dose-response effect of cannabinoids in acute neuropathic pain is consistent with the previous body of research [54].

Nociceptive Pain

Cannabis has not been found effective in acute nociceptive pain and has shown a biphasic dose-response effect with acute neuropathic pain [54]. However, chronic pain results from the development of abnormal sensory processing and other alterations in peripheral and CNS pain pathways [173]. The endocannabinoid receptor complex interacts with signaling pathways and pain circuitries expressing abnormal function in chronic pain, accounting for therapeutic effect not seen in acute pain [55].

Clinical trials of cannabinoids in patients with chronic pain due to rheumatoid arthritis, fibromyalgia syndrome, or cancer pain found statistically significant pain relief consistently around 30% in magnitude [174]. When considered alone, changes in

pain scores understate the extent of overall relief in these patients, because improved mood, sleep, coping, and quality-of-life scores have been consistently reported with cannabis and cannabinoids. Patients with fibromyalgia and clinically relevant depression showed greater benefit from cannabinoids than non-depressed patients with fibromyalgia [54].

Reducing Opioid Requirements

Studies of chronic non-malignant pain have found significant pain relief, reduced bother from pain, and prevention or reduction of opioid tolerance with cannabinoid addition to opioid therapy [175; 176]. An RCT with patients with severe cancer pain found cannabinoid addition to opioid therapy led to pain level reduction of 30% to 50% in 43% of patients [54; 177]. In patients with pain from chronic progressive multiple sclerosis, HIV-related neuropathy, or spinal trauma pain poorly controlled with high-dose opioids, one study found adding smoked cannabis led to opioid dose decreases of 60% to 100% and improvements in pain relief and function [178]. Abrams studied the effect on pain from giving four days of vaporized cannabis to 21 patients with mixed persistent chronic pain despite stable long-term use of morphine sustained-release (SR) or oxycodone SR (mean dose: 62 mg and 53 mg, respectively) [110]. Cannabis slightly reduced morphine levels, had no effect on oxycodone levels, and reduced pain by roughly 30%. A survey of 29 medicinal cannabis patients with chronic pain found that of the eight using cannabis as their sole analgesic, all had been prescribed but abandoned opioids for cannabis due to the greater perceived pain relief, fewer side effects, or absence of problematic opioid use risk [179].

Combining opioids and cannabis in pain therapy offers the added potential advantage of synergistic analgesic action that decreases the dosage requirements and side effects of both agents. Such an approach exploits the considerable functional interaction between endogenous opioid and cannabinoid systems and may also reduce the development of tolerance with both agents [164].

NEUROPSYCHIATRIC DISORDERS

Multiple Sclerosis and Spasticity

Spasticity is a core symptom of multiple sclerosis, is common after stroke and with other neurologic conditions, and greatly limits movement, activities of daily living, and participation in life by those afflicted. Oral antispasmodic agents are of limited effectiveness, and beneficial treatment options for spasticity have not significantly expanded since the late 1990s [180]. Consequently, many patients with multiple sclerosis have sought relief through cannabis use. The oromucosal cannabinoid spray nabiximols appears efficacious in multiple sclerosis but is not yet approved for clinical use in the United States [181]. Several clinical trials of cannabis in multiple sclerosis have been performed, and these studies have demonstrated cannabis efficacy in reducing spasticity and pain [182; 183]. Cannabis-based medicine was effective in reducing pain and sleep disturbance in patients with multiple sclerosis and central neuropathic pain in one trial, while other RCTs demonstrated significant improvements in spasticity, disability, cognition, mood, sleep, and fatigue [184; 185; 186]. A 2004 study also found that cannabis helped alleviate bladder dysfunction, a problematic multiple sclerosis symptom [187]. A double-blind, placebo-controlled crossover study randomized patients with multiple sclerosis to smoke 4% THC or placebo cannabis cigarettes once daily for three days [183]. The findings of significant objective improvement in pain and spasticity differed from earlier trials showing significant improvement in patient perceptions but not objective measurements of spasticity [183]. Side effects have been acceptable to patients, and no serious safety concerns have emerged. Preclinical studies suggest a positive effect on the underlying disease processes in multiple sclerosis, evidence of an anti-inflammatory effect, and facilitation of remyelination and neuroprotection [188].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Academy of Neurology asserts that clinicians might offer oral cannabis extract to patients with multiple sclerosis to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain).

(https://www.aan.com/Guidelines/home/GuidelineDetail/641. Last accessed November 11, 2020.)

Level of Evidence: A (Established as effective for the given condition in the specified population.)

Post-Traumatic Stress Disorder

Numerous case reports describe substantial reduction in PTSD symptoms with cannabis use [189]. An open-label study of nabilone in 47 patients with treatment-refractory PTSD-associated nightmares found cessation or significantly reduced nightmare intensity in 72% of participants and diminished daytime flashbacks and night sweats and/or improved sleep duration and quality for some [190]. More robust research supporting the safety and efficacy of this use is lacking [191].

Seizure Disorders

As noted, cannabis can be bred to overexpress CBD in order to avoid psychoactive effects. In one study, CBD-enriched cannabis was administered to 19 children with treatment-refractory epilepsy (after an average of 12 pre-study antiepileptic drugs) and their parents were interviewed to assess efficacy. Of the 19 patients, 84% showed reduced seizure frequency, 11% became completely seizure-free, 42% showed greater than 80% seizure reduction, and 32% showed a 25% to 60% seizure reduction. Other beneficial effects included increased alertness, elevated mood, and improved sleep, and side effects included drowsiness and fatigue. In 2018, the FDA approved purified cannabidiol for use in patients with Lennox-Gastaut and Dravet syndromes, but until recently, most published studies were relatively short-term (12 to 16 weeks) [77; 192; 193]. The objective of a 2019 study was to evaluate the long-term safety, tolerability, and efficacy of cannabidiol in children with epilepsy [193]. This open-label prospective study enrolled 26 children 1 to 17 years of age with refractory epilepsy, most with genetic epilepsies with daily or weekly seizures and multiple seizure types. All of the children were refractory to prior antiepileptic drugs and were, on average, taking two antiepileptic drugs. The duration of therapy ranged from 4 to 53 months (mean: 21 months). Adverse events were reported in 21 patients (80.8%) and included reduced appetite, diarrhea, and weight loss. Serious adverse events were reported in six patients (23.1%) and included status epilepticus, catatonia, and hypoalbuminemia. Fifteen patients (57.7%) discontinued cannabidiol for lack of efficacy. At 24 months, 9 of the original 26 patients (34.6%) remained on cannabidiol as adjunctive therapy. Of these, seven reported a more than 50% reduction in motor seizures and three remained seizure free [193].

Fibromyalgia

A matched case control study of medicinal cannabis use for symptom control in fibromyalgia found patient accounts of cannabis efficacy in alleviating pain, sleep disturbance, stiffness, problematic mood and anxiety, and headache, and objectively measured significant improvements in pain, stiffness, relaxation, and well-being [194]. An estimated 68% of participants experienced a reduction in standard therapies following cannabis initiation. Frequent side effects were somnolence, dry mouth, sedation, and dizziness. Significantly higher mental health-related quality of life scores were found in medicinal cannabis users compared with non-users [194].

GASTROINTESTINAL DISORDERS/DYSFUNCTION

Irritable Bowel Syndrome and Crohn Disease

In one study of patients with chronic irritable bowel syndrome, inhaled cannabis for three months led to improvements in quality of life, disease activity, and weight gain [195]. Observational study data in patients with Crohn disease suggest that cannabis helps alleviate disease symptom severity and reduces the requirements for other medications and/or the need for surgery [196].

Nausea and Vomiting

Chemotherapy-induced nausea and vomiting was very difficult to manage before the introduction of 5-HT3 receptor antagonists. However, 5-HT3 antagonists are not very effective in blocking acute nausea and are ineffective in reducing delayed (24 hours or more) and anticipatory (conditioned) nausea and vomiting. The drugs of the NK1 receptor antagonist class are more effective with delayed as well as acute vomiting, although they are much less effective in reducing nausea. Nausea is the most distressing symptom experienced by chemotherapy patients because it is a continuous sensation, and as many as 20% of patients with cancer discontinue chemotherapy because current standard agents fail to control nausea [98; 197]. A vast body of anecdotal evidence from the past 150 years as well as preclinical and clinical trial results strongly indicate a valuable role for cannabis in controlling nausea and vomiting caused by cytotoxic drug administration or secondary to another primary medical condition [98].

Most studies showing cannabinoid efficacy have used oral synthetics. The synthetic THC analogue nabilone and the synthetic THC dronabinol received initial regulatory approval for chemotherapy-induced nausea and vomiting based on improved outcomes over standard antiemetics used in the 1980s [98]. An older study of Δ8-THC, a close but less psychoactive relative of Δ9-THC, in pediatric patients with chemotherapy-induced nausea and vomiting found effective suppression of nausea and vomiting with negligible side effects [95]. More recently, an RCT with adults experiencing chemotherapy-induced nausea and vomiting found dronabinol comparable to the 5-HT3 antagonist ondansetron and superior to placebo [98; 198].

An additional rationale for cannabis use in chemotherapy-induced nausea and vomiting involves the principle of optimizing treatment by combining agents that inhibit multiple neurotransmitter pathways that mediate nausea and vomiting reflexes. Cannabinoids have known activity in many of these systems and can effectively compensate for the deficiencies of 5-HT3 antagonists and NK1 receptor inhibitors in preventing nausea and delayed and breakthrough chemotherapy-induced vomiting. Because cannabidiol does not induce psychotropic effects, its potential role as an antiemetic for patients undergoing chemotherapy is being investigated [199]. The potential role of smoked cannabis in rapidly alleviating breakthrough nausea and vomiting is especially promising given the findings of strong patient preference for smoked cannabis over oral therapies in a number of comparative clinical trials [3].

A study comparing 748 patients with cancer who smoked cannabis before and after chemotherapy with 345 patients using dronabinol found a reduction in nausea and vomiting of 70% to 100% with cannabis compared with 76% to 88% with dronabinol [200]. Oral cannabinoids may be less effective than sublingual or inhaled cannabis in chemotherapy-induced nausea and vomiting, and most patients prefer smoked marijuana over oral synthetic cannabinoids [201]. Several reasons account for this preference:

- The advantages and ease of self-titration with smoked cannabis
- Difficulty in swallowing pills when experiencing emesis
- Rapid speed of onset compared with oral delivery
- The combined therapeutic effects of additional cannabinoids in smoked cannabis

A meta-analysis of cannabinoid efficacy in chemotherapy-induced nausea and vomiting found superior antiemetic efficacy of dronabinol, nabilone, levonantradol (not approved for use in the United States), and smoked cannabis compared with conventional drugs and placebo [202].

Smoked cannabis has also been shown to improve non-chemotherapy medication adherence in which nausea and vomiting are common side effects. In a study of 258 patients receiving antiretroviral therapy for HIV infection, the subgroup of patients experiencing moderate-to-severe nausea who used marijuana were significantly more adherent to their regimen than non-marijuana users (75% vs. 48%).

Alcohol use, the use of other illicit drugs, and marijuana use in those without nausea were associated with lower adherence [203].

HEPATITIS C THERAPY

Until 2014, interferon/ribavirin combination therapy was the sole treatment for hepatitis C virus infection, and it remains widely used. However, patient intolerability of side effects has been a substantial barrier to treatment success. Most patients experience significant side effects that can include debilitating fatigue, headaches, nausea, anorexia, clinical depression, and insomnia. Patients usually require adjunctive pharmacotherapy for side-effect management, but relief is often incomplete, leading to dose reduction or termination. Illicit cannabis is used by some patients to lessen side effects.

A prospective study compared 71 patients with hepatitis C receiving interferon/ribavirin who either used cannabis (31%) or did not use cannabis (69%) for side effect relief [204]. Several statistically significant differences were found between the cannabis- and non-cannabis using patients. Five percent of cannabis users vs. 33% of non-users discontinued therapy. Compared with 18% of non-users, 54% of cannabis users had a sustained virologic response, with post-treatment virologic relapse rates of 14% in cannabis users vs. 61% in non-users. Finally, 86% of cannabis users were treatment-adherent, while 59% of non-users adhered to treatment. Occasional and regular cannabis users did not differ in adherence or sustained virologic response. The authors conclude that moderate cannabis use may offer significant benefit to some patients enduring the frequently debilitating medication regimen for hepatitis C and that an additional biologic benefit beyond adherence promotion cannot be ruled out [204].

SLEEP DISORDERS

Sleep disturbances contribute to greater pain, disease activity, mood disturbance, and disability in patients with chronic pain, and restoring normal sleep improves pain and mood disorders associated with uncontrolled pain and sleep impairment [54]. However, drugs used for sleep induction (such as benzodiazepines) increase rates of sleep-disordered breathing and elevate the risk of respiratory depression and fatal respiratory arrest when combined with opioids, antihistamines, or alcohol. Unlike sedative-hypnotics, cannabinoids suppress sleep-related apnea and do not enhance opioid-induced respiratory depression [37]. Research in chronic pain patients has consistently shown beneficial cannabinoid effects on sleep quality [54].

CANCER- AND HIV-ASSOCIATED ANOREXIA AND WEIGHT LOSS

Anorexia, early satiety, weight loss, and cachexia are prevalent in late-stage cancer and advanced HIV disease. Most standard treatments are ineffective, but many patients show favorable response with marijuana and cannabinoids [83]. A 2005 survey of HIV-positive medical marijuana users found decreased nausea and other burdensome symptoms in 93% of participants and substantial improvement of nausea in 56% [4]. A double-blind clinical trial of HIV-positive patients found smoked cannabis increased daily caloric intake and body weight, with few adverse effects [205]. Benefits from smoked cannabis reported by 252 patients with HIV/AIDS included relief of anxiety and/or depression (57%), improved appetite (53%), increased pleasure (33%), and pain relief (28%). However, recent use of marijuana was strongly associated with severe nausea [206]. Long-term data on the sustained effect of cannabis and cannabinoids for the treatment of HIV/AIDS-associated anorexia are lacking [207].

A review of cannabinoid use in patients with cancer found a beneficial effect in stimulating appetite in patients who were receiving chemotherapy or experiencing pain [208]. Interestingly, the results of several preclinical and preliminary clinical testing studies have suggested that cannabinoids inhibit tumor and/or malignant cell growth in pancreatic, lung, leukemic, melanoma, oral, and lymphoma cancers and other malignant tumors [209].

GLAUCOMA

High intraocular pressure is a risk factor for glaucoma, and smoked cannabis has been found to reduce pupil constriction, conjunctival hyperemia, and intraocular pressure by approximately 25% in those with normal range intraocular pressure with visual field changes, healthy adults, and patients with glaucoma [210]. However, the short duration of effect (three to four hours), side effect profile (including potentially lowering blood supply to the optic nerve by lowering systemic blood pressure), and lack of evidence regarding impact on the course of the disease limit the potential positive impact of cannabis for the treatment of treatment-resistant glaucoma [210; 211]. The American Glaucoma Society recommends against the use of smoked cannabis for the treatment of glaucoma, and the IOM and the American Academy of Ophthalmology concluded that smoked cannabis is neither a safer alternative nor offers increased benefits compared with conventional pharmaceutical agents [211]. More research is necessary to determine if topical administration may confer greater benefits.

NATURALISTIC STUDIES OF MEDICAL CANNABIS USE

Naturalistic studies have been performed in persons illicitly using medicinal cannabis for symptom relief over diverse diseases and conditions. These studies provide important background information on medicinal cannabis users and improved understanding of limitations with standard therapeutics [15]. Diverse backgrounds have been found in medical user members of Cannabis Buyer's Cooperatives. A 1998 study of 1,500 cooperative members in Oakland and Los Angeles found illicit cannabis was used for HIV/AIDS in 62% to 70% of members and cancer in 4% to 10%. In the remaining Oakland members, another 10% reported using cannabis for pain or arthritis, 8% for mood disorders, 6% for neurologic symptoms, 4% for glaucoma, and 6% for "other" conditions; in remaining Los Angeles members, 20% used cannabis for "other" diagnoses, including neurologic diseases, glaucoma, hepatitis, cardiovascular disease, and renal failure [212]. These patients differed from those in a 2005 UK study of 2,969 adults who used cannabis for symptom relief in chronic pain (25%), multiple sclerosis (22%), depression (22%), arthritis (21%), and neuropathy (19%) [213]. In another study of 209 Canadians using cannabis to control chronic (median: eight years) non-cancer pain, the most frequent pain type was trauma or postsurgical pain (51%), with the most frequent pain sites being neck/upper body pain (68%) and myofascial pain (65%) [214]. Frequency of cannabis analgesic use was evenly distributed over the intervals of more than once daily, once daily, weekly, and rarely. Greatest symptom improvement was in pain, sleep, and mood [214]. In a report involving 220 Canadian patients with multiple sclerosis, 36% had used cannabis prior to legalization and 14% continued its use for symptom relief; the greatest improvements were in pain, stress, sleep difficulties, mood, and muscle spasm/stiffness [215]. Another study found that 80% of patients with limitations in activity or function from chronic illness attained consistent pain reduction, on a 1–10 scale, ranging from 7 to 10 [32].

ALTERNATIVES TO CANNABIS

Opponents of medicinal cannabis often state that dronabinol provides the alleged benefits of smoked cannabis and fewer risks, essentially arguing that any benefit is the result of Δ9-THC. However, dronabinol is not a realistic substitute for inhaled cannabis for a number of reasons. Many patients describe dronabinol's effect as unpleasant, due to excessive sedation and an overwhelming psychoactive effect. This is likely from its 100% THC content versus the 10% to 20% THC (and variable CBD) content in natural cannabis [216]. Also, dronabinol is often poorly absorbed as an oral agent, and the dosage is difficult to monitor and control. Patients with severe nausea and vomiting, or who otherwise cannot swallow, are unable to ingest oral medication (or keep it down). Cannabis possesses therapeutic constituents in addition to Δ9-THC, and the rapid onset of effect attained by inhalation can provide quick relief and allow dose titration unable to be achieved with slower-onset oral agents [83].

INDICATIONS AND PRACTITIONER CONSIDERATIONS

INDICATIONS

As noted, cannabis is generally recommended for patients in whom standard therapies have been ineffective or intolerable. Appropriate indications for medical cannabis have most recently been formalized by the State of New York, the OMC in the Netherlands, and Health Canada and include [217; 218; 219]:

- Disorders of pain and spasticity, including intractable spasticity, multiple sclerosis, and spinal cord damage or injury
- Chronic neuropathic pain, including nerve damage, phantom limb pain, facial neuralgia, and postherpetic neuralgia
- Pain from cancer and HIV/AIDS
- Nausea and vomiting from chemotherapy, radiotherapy, and/or medication for HIV and hepatitis C
- Neuropsychiatric disorders, including tics associated with Tourette syndrome, epilepsy, neuropathy, Parkinson disease, and PTSD
- Autoimmune conditions, including arthritis, lupus, and Crohn disease
- Palliative treatment of cancer and AIDS to stimulate appetite, avoid weight loss, and reduce debilitation and wasting syndrome
- Treatment-resistant glaucoma
- A debilitating symptom associated with a medical condition or the medical treatment of that condition, other than those described above

DOSE AND ADMINISTRATION GUIDANCE

The ideal dosage of cannabis or THC varies by condition and patient characteristics. Inhaled cannabis is not a preferred route of administration due to difficulty with dosing, risk of respiratory damage, and multi-component composition [219]. For the treatment of refractory pain, nabiximols spray is preferred over smoked cannabis. The initial recommended dose is one spray sublingually at bedtime and not more than 12 sprays daily [219]. For the treatment of chemotherapy-induced nausea and vomiting, nabilone is preferred over cannabis [219]. The recommended initial oral dose is 0.25–0.5 mg at bedtime and not more than 6 mg/day [219]. Studies conducted in Israel and the Netherlands found the average dose for patients in their medical cannabis programs was 1.5 g/day and 0.68 g/day, respectively [27; 220].

The recommended initial dose of dronabinol is 2.5 mg twice daily, but this may be reduced to 2.5 mg once daily at bedtime if the patient is unable to tolerate twice-daily dosing [77]. This may be titrated up to effect to a maximum of 20 mg per day. Nabilone for chemotherapy-induced nausea and vomiting is started at 1–2 mg twice daily and may be increased to a maximum of 6 mg/day in three divided doses [77].

In all cases, it is important to begin with the lower dose in the range and increase if needed. If the starting dose is tolerated but the desired effects are not achieved, slowly increase the dose [82; 219]. One should keep in mind that the therapeutic dose is usually lower than the recreational dose. For medicinal purposes, the OMC recommends vaporized or oral ingestion; smoking is not recommended [82]. Patients orally ingesting cannabis or cannabinoids should be advised of the slow onset and the need to ingest small amounts spaced several hours apart [14].

Vaporizing

Though it is often recommended in discussions of medical marijuana use, many healthcare professionals are not familiar with the process of administering cannabis through vaporizing. In essence, active cannabis ingredients can be vaporized if cannabis is heated and inhaled without combustion. The right temperature is reached when vapor is just visible as a light mist, but no smoke has formed, usually at a temperature of 180°C to 195°C. Using this method, the same cannabis can be used two to three times. In most cases, the recommended initial dosing is one to two times per day, with a minimum of 5 to 15 minutes between inhalations. Patients may need to inhale a few times, until the desired effect is reached or side effects occur. It may take up to two weeks to achieve steady-state THC concentrations and full therapeutic effect.

Tea

As discussed, a cannabis tea may be used to ingest medical marijuana, though the limited THC bioavailability and lack of water solubility make this a less attractive option in most cases. To brew the cannabis tea, 0.5 g cannabis is boiled in a pint of water for 15 minutes. The plant material is then strained out of the tea and sweeteners are added. The addition of a substance containing fat (e.g., milk powder) can improve the availability of THC in the tea. The tea may be kept refrigerated for up to five days. The usual initial dose is one cup in the evening, though if the effects are insufficient after two weeks, an additional cup (usually in the morning) may be added.

CONTRAINDICATIONS AND PRECAUTIONS

At this time, experts recommend limiting medical cannabis use to adults older than 18 years of age [14; 82; 218]. There are several other contraindications to the use of medical marijuana, including [14; 218]:

- Current, past, or family history of schizophrenia or other psychotic disorders
- History of hypersensitivity to cannabinoids or smoke
- Severe cardiopulmonary disease
- Severe liver or renal disease
- Pregnancy or planned pregnancy
- Breastfeeding

Cannabis may be considered with caution for patients with the following factors when alternatives have been ineffective/poorly tolerated, the benefit/risk ratio closely evaluated, and with sufficient monitoring [14; 218]:

- Smoked cannabis in patients with asthma or COPD
- History of substance abuse
- Non-psychotic psychiatric condition (e.g., anxiety, panic attacks)
- Current CNS depressant therapy

PATIENT EDUCATION

If a patient is prescribed a cannabinoid or medical cannabis, he or she should be advised of possible memory impairment and instructed to report any mental or behavioral changes. In addition, operating a vehicle or heavy machinery is not recommended after having taken the drug, and patients should limit or abstain from alcohol.

All patients should be monitored for outcomes, similar to the processes used for opioid follow-up monitoring. Any concomitant medications and drug interactions should also be monitored. For example, there is little evidence of clinically significant CYP450 interactions, but co-administration may potentiate somnolence [116; 165; 221]. Side effects should be noted and reported; however, it is important to note that tolerance may develop over time to side effects of mild-to-moderate severity. Smoking or vaporization should cease if a patient begins experiencing disorientation, dizziness, ataxia, agitation, anxiety, tachycardia and orthostatic hypotension, depression, hallucinations, or psychosis [14].

For patients who are not proficient in English, it is important that information regarding the benefits and risks associated with the use of medical marijuana and other cannabinoids be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

CONCLUSION

Medical marijuana has become a hot topic in health care. Initiatives to either legalize or prohibit marijuana use for medical purposes are being legislated by politicians or presented to voters in numerous municipalities. The preponderance of information on this subject seems to come from highly visible individuals or groups who either vehemently oppose or passionately advocate legal access to medical cannabis. What is most needed is a comprehensive presentation of the scientific facts from a dispassionate, evidence-based perspective. This course has reviewed the body of research on medical cannabis to provide the most current information on potential indications, pharmacology and mechanism of action, acute and chronic side effects, and contraindications for medicinal cannabis. A clear understanding of the potential uses of cannabinoids in the treatment of various medical conditions will benefit patients and healthcare providers alike.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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