PUBLIC HEALTH IN THE 21ST CENTURY

THE SCIENCE OF
MEDICAL CANNABIS

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biomedical
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NOTICE TO THE READER

For my wife Holly and sons Adam and Seth, who encourage me to take on projects that promote core values of humanity.

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Joseph J. Smulsky

PREFACE

The cultural, scientific and legislative divide created by vigorous debates over the legalization of medical marijuana is giving way to a new synergy among community stakeholders across the United States. The goal is to improve access to medical marijuana for patients with refractory debilitating neurological disorders, cancer, and chronic pain as an alternative to ineffective pharmacotherapy and potentially addictive pain medications. The ultimate test of our nation's resolve to ensure the welfare of our sickest patients is the enactment and implement of effective public health reform in the area of medical marijuana, also known as medical cannabis.

This book evolved out of the present need for a definitive volume on the science and public health aspects of medical cannabis to fuel this national narrative. The ethnographic research presented in the concluding chapter was inspired by Professor Miriam W. Boeri and colleagues, at Bentley University in Waltham, MA. They examined views of community stakeholders including medical marijuana dispensary entrepreneurs, health care professionals, and patients in a state that legalized medical marijuana in 2013, yet there continued to be confusion and misunderstandings in the interpretation and implementation of medical marijuana guidelines during the period of policy shifts. Apparent gaps in policy development and implementation signaled the urgency for a comparison study addressing stakeholder views in New York State, where its medical marijuana program

has legally dispensed the drug since 2014. The resulting pilot study was carried out in the Division of Health Policy and Management of the City University of New York School of Public Health with stakeholders from Vireo Health of New York. The research model incorporated ethnographic and grounded methodologies to detail the views of physicians, pharmacists, educators, patients, and entrepreneur stakeholders; with triangulation of data and application of dominant themes into a socioecological framework model to identify areas of public health policy reform. The findings of this study detail that New York, like other states that recently legalized the dispensation of medical marijuana, faces challenges beyond policy transparency, communication and education explicitly to improve the implementation process for applying and registering medical cannabis dispensaries, referring physicians, and qualified patient recipients.

On a personal note, I have had the good fortune of interacting with thought-provoking medical students, neurology trainees, public health doctoral students, and professors at New York University School of Medicine in the Department of Neurology; and City University of New York in the School of Public Health, Department of Health Policy and Management, embracing the highest ethical standards in medical and public health practice and research. In the end, however, it is my patients who teach me the most valuable lessons in empathy and humility that are ultimately so vital to their welfare and care.

Many thanks to Ms. Lauren Bangug, Clinical Coordinator, for assisting in the preparation of the final manuscript.

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New York, NY
September 27, 2018

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ABBREVIATION LIST

2-AG	2-arachidonoylglycerol
5-HT3	serotonin type 3 receptor
5-HT1B	5-hydroxytryptamine receptor 1B
Δ^9-THC	(-)-trans-Δ-9-tetrahydrocannabinol
Δ^9-THCA	Δ-9-tetrahydrocannabinolic acid
AAN	American Academy of Neurology
ACEA	arachidonoyl-21-chloroethylamide
AChE	acetylcholinesterase
ACPA	arachidonoyl cyclopropamide
AD	Alzheimer's disease
ADL	activities of daily living
AEA	N-arachidonoylethanolamine, or anandamide
AIBP	AEA intracellular binding proteins
AIDS	acquired immunodeficiency syndrome
AMP	adenosine monophosphate
AMPK	AMP-activated protein kinase
ANOVA	analysis of variance
ANS	autonomic nervous system
ANSI	American National Standards Institute
API	active pharmaceutical ingredient

ASR	age-standardized rates
ATP	adenosine triphosphate
BBB	blood brain barrier
BCP	β-caryophyllene, or caryophyllene
BPP	benzopyranoperidine
BPSD	behavioral and psychological symptoms of dementia
CACS	cancer anorexia-cachexia syndrome
c-AMP	cyclic AMP
CB	cannabinoid
CBC	cannabichromene
CBCV	cannabichromevarin
CBD	cannabidiol
CBDA	cannabidiolic acid
CBDV	cannabidivarin
CBG	cannabigerol
CBGA	cannabigerolic acid
CBGV	cannabigerovarin
CBM	cannabis-based medicine
CBN	cannabinol
CD4+	T-helper cell
CD8+	cytotoxic cell
CE	cannabis extract
CI	confidence intervals
CUNY	City University of New York
CINV	chemotherapy-induced nausea and vomiting
CNS	central nervous system
CO_2	carbon dioxide
CSD	cortical spreading depression
CT-3	ajulemic acid
DA	divarinic acid
DEA	Drug Enforcement Administration
DFCR	Doctors for Cannabis Regulation
DIS	dissemination in space

DIT	dissemination in time
DMAPP	dimethylallyl pyrophosphate
DNA	deoxyribonucleic acid
DOX	deoxyxylulose pathway
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EOAD	early-onset Alzheimer's disease
ERK1/2	extracellular signal regulated kinase-1 and -2
EtOH	ethanol
FAAH	fatty acid amide hydrolase
FAAH1	fatty acid amide hydrolase-1
FDA	Food and Drug Administration
FID	flame ionization detector
F/S	feed-to-solvent
GABA	γ-Aminobutyric acid
GABAergic	gamma-aminobutyric acid secreting
GC	gas chromatography
GLC	gas-liquid chromatography
GOT	geranyl-pyrophosphate:olivetolate geranyltransferase
GPP	geranylpyrophosphate
GW	GW405833
H_2O_2	hydrogen peroxide
HCA	hierarchical clustering analysis
hCB1R	human CB_1 receptor
HD	hydrodistillation
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HSP	heat shock protein
ICF	International Classification of Functioning, Disability and Health
IPP	isopentenyl pyrophosphate
IVIG	intravenous immune globulin
JNK	c-Jun N-terminal kinase

JWH133	CB$_2$ receptor agonist
MAPK	mitogen activated protein kinase
MGC	medical-grade cannabis
MM	medical marijuana
MMD	medical marijuana dispensary
MML	medical marijuana legalization
MOH	medication overuse headache
MOVE	mobility improvement
MRI	magnetic resonance imaging
MS	mass spectroscopy
MS	multiple sclerosis
MSS	MS-related spasticity
MVA	mevalonate pathway
NDPH	new daily persistent headache
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NIB	synthetic nitrogen analog of tetrahdrocannabinol
NK	natural killer
NMDA	N-methyl-D-aspartic acid
NPS	neuropsychiatric symptoms
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drugs
NTG	nitroglycerin
OA	olivetolic acid
OAB	overactive bladder
OCE	oral cannabis extract
OPLS-DA	orthogonal partial least squares discriminant analysis
OSHA	Occupational Safety and Health Administration
PAG	periaqueductal gray
PCA	principal component analysis
PCR	polymerase chain reaction
PF-04457845	FAAH1 inhibitor
PLS-DA	partial least squares discriminant analysis

PNS	peripheral nervous system
PPAR	proliferator-activated receptor
PPMS	primary progressive MS
PTSD	post-traumatic stress disorder
PY	person-years
RCT	randomized controlled trials
ROS	reactive oxygen species
RRMS	relapsing-remitting MS
SD	steam distillation
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SEF	socio-ecological framework
TAC	Trigeminal autonomic cephalgias
TEM	transmission electron microscopy
THC	tetrahydrocannabinol
THCA	tetrahydrocannabinolic acid
THCAS	THCA synthase
THCV	tetrahydrocannabivarin
TLE	temporal lobe epilepsy
TRPV1	transient receptor potential vanilloid-1
US	United States
VAS	visual analog scale
QoL	quality of life
YLD	years lived with disability

FOREWORD

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September 3, 2018

We are at a pivotal juncture in medical history deciphering how to define our relationship with a plant that has long been our evolutionary companion. I commend Dr. David S. Younger for writing The Science of Medical Cannabis, the definitive work on the science and public health aspects of medical marijuana, that will be the new industry standard. Its publication will inform New York State and other states' medical cannabis programs regarding fundamental measures for achieving quality and performance in health delivery services. In addition, The Science of Medical Cannabis will serve as an invaluable resource for patients, pharmacists, public policy officials, educators, and physicians. It will help all stakeholders in the system make informed decisions about a pharmaceutical that is entrenched in stigmatization. I have seen with my own eyes the tremendous potential cannabis has as a treatment modality. It is my sincere hope that Dr. Younger's book will serve as an indispensable tool to support the ultimate goal of all health professionals in serving their patients, for some in the journey to recapture their prior health and vitality, while for others in their quest to find the safest way to alleviate pain and suffering.

Chapter 1

OVERVIEW OF MEDICAL CANNABIS

INTRODUCTION

Imagine you are sick with a chronic condition that either escapes understanding, such as chronic pain, or worse, one for which there is no cure such as lethal cancer. In the best scenario, you hope for effective management by your physicians and their pharmaceutical options, yet the choices are either limited or the ones you try may make you feel sicker.

Consider also that the Food and Drug Administration (FDA) has little say so in the approval of a medication acting more as a marketing agent after the pharmaceutical industry establishes its safety in clinical trials, and you will find that we have not yet started an open dialogue about medical marijuana. This is unfortunate because there is an extensive literature about the medical applications for cannabis. This article is an overview of medical cannabis. Subsequent chapters will examine detailed aspects of the history, speciation, genetic structure, pharmacology, pharmacokinetics, dosing, administration, and safety of cannabinoid agents, and their role in maintaining homeostasis for the body during chronic illness. Aspects of the emerging medical marijuana industry will be reviewed.

HISTORICAL ASPECTS

Cannabis sativa (cannabis) is among the earliest plants cultivated by man. The history of cannabis as a medicine was reviewed by Zaydi [1]. The ancient Chinese used it as a medicine as cited in the world's oldest pharmacopoeia, the pen-tsar chin, compiled during the first century. The founder of Chinese surgery (A.D. 110–207), used a compound of the plant, taken with wine, to anesthetize patients during surgical operations]. Its use in India was also widely disseminated, assigned sacred virtues, as well as use for medicinal and recreational purposes. The Atchara Veda, a collection of sacred texts of unknown author, mentions cannabis as one of five sacred plants, referring to it as a source of happiness, donator of joy and bringer of freedom. The plant's psychoactive effects were well-known in India, due to the way it was prepared whether weakly formulating its dry leaves from which flowers were carefully removed, to the stronger preparation of Ganja, extracted from the plant's flowers. The strongest of them was Charis, exclusively made from the resin covering the flowers, assuring the most potent availability of active cannabinoids. It is now known that the secreting hairs of the plant are located mainly on the female-plant's flowers and, in a smaller amount, on the leaves of its superior third. Solitary resin glands most often form at the tips of the trichome stalks. Such glands have a considerable amount of active cannabinoids. Breaking the glands liberates the active cannabinoids. Such preparations were used for its analgesic (neuralgia, headache, toothache), anticonvulsant (epilepsy, tetanus, rabies), hypnotic, tranquilizer (anxiety, mania, hysteria), anesthetic, anti-inflammatory (rheumatism and other inflammatory diseases), antibiotic (topical use on skin infections, erysipelas, tuberculosis), ant parasitic (internal and external worms), antispasmodic (colic, diarrhea), digestive, appetite stimulant, diuretic, aphrodisiac, antitussive and expectorant (bronchitis, asthma) medicinal benefits.

From the Christian era to the 18th century the medical use of cannabis spread to the Middle East, Africa and to Arabia, where well-known physicians mentioned cannabis in their medical compendia's as a diuretic, digestive, and anti-flatulent, and for use to clean the brain, and soothe pains.

In the Americas, the use of cannabis probably began in South America in the 16th century, where the plant seeds reached Brazil. In Europe, cannabis was cultivated exclusively for fibers. By the 19th century, European physicians used cannabis in their medications. However, the effective introduction of cannabis in Western medicine occurred in the midst 19th century through the works of William B. O'Shaughnessy, an Irish physician, and Jacques-Joseph Moreau, a French psychiatrist.

In his book, O'Shaughnessy described various successful human experiments using cannabis preparations for muscular spasms of tetanus [2]. Moreau experimented systematically with different cannabis preparations, first on himself and later on his students, eventually publishing a complete description of the acute effects of cannabis [3]. These two types of medical interest for cannabis, concerning its psychoactive effects (as an experimental psychotomimetic) and its therapeutic use, continued.

In the second half of the 19th century, over 100 scientific articles were published in Europe and the United States about the therapeutic value of cannabis. The climax of the medical use of cannabis by Western medicine occurred in the late 19th and early 20th century when various laboratories marketed cannabis extracts or tinctures, such as Merck (Germany), Burroughs-Wellcome (England), Bristol-Meyers Squibb (United States), Parke-Davis (United States), and Eli Lilly (United States) [4]. By the beginning of the 20th century, the medicinal benefits of cannabis includedanalgesic its sedative or hypnotic actions for insomnia, senile insomnia, melancholia, mania, delirium tremens, chorea, tetanus, rabies, hay fever, bronchitis, pulmonary tuberculosis, coughs, paralysis agitans, exophthalmic goiter, spasm of the bladder, and gonorrhea. Its analgesic qualities were used for treatment of migraine, eye-strain, menopause, brain tumors, tic douloureux, neuralgia, gastric ulcer, gastralgia (indigestion), tabes, multiple neuritis, uterine disturbances, dysmenorrhea, chronic inflammation, menorrhagia, impending abortion, postpartum hemorrhage, acute rheumatism, eczema, senile pruritus, tingling, formication and numbness of gout, and dental pain. And other uses to improve appetite and digestion, for the pronounced

 anorexia following exhausting diseases, gastric neuroses, dyspepsia, diarrhea, dysentery, cholera, nephritis, hematuria, diabetes mellitus, cardiac palpitation, and vertigo, sexual atony in the female, and male impotence.

Legal restrictions limited the medical use and experimentation of cannabis in the United States as the result of a campaign of the Federal Bureau of Narcotics, and the 1937 Marihuana Tax Act law under which anyone using the plant was required to register and pay a tax of a dollar an ounce for medical purposes, and 100 dollars an ounce for any other use. The Supreme Court gave the States the right to control commercial transactions and, in practice, meant banning the use of cannabis after which it was removed from the American pharmacopoeia in 1941.

In the second half of the 20th century, cannabis reached great social importance due to the explosion of its consumption for hedonistic purposes. During the 1960's, its recreational use rapidly spread among the younger ranges of the population throughout the Western world. In 1964, the chemical structure of (-)-trans-delta-9-tetrahydrocannabinol, abbreviated Δ^9-THC or THC, was identified by Gaoni and Mechoulam [5], contributing to the proliferation of studies of the active constituents of cannabis [6]. The number of publications about cannabis has been continuously growing, attesting the tremendous interest in research involving the herb. There are studies, in different phases, studying the therapeutic effects of THC in diverse medical conditions, and for different therapeutic indications, with some already proven. Other cannabinoids are also under investigation for their therapeutic benefits in epilepsy and as neuroprotectors in inflammatory autoimmune brain disorders.

In July 2014, New York became the 23rd state (plus Washington DC) to legalize personal marijuana possession and its consumption for putative medical purposes. The American public was ready to legalize doctor-supervised medical marijuana as evidenced by a 2014 poll in which 86% favored legalization for seriously ill patients. As of last year, 23 states passed medical marijuana laws intended to decriminalize possession for personal

use or so-called legitimate medical uses, with more states on the way, while Colorado, Washington, Alaska, Oregon, and Washington DC went further by legalizing the sale and possession for personal recreational use.

SPECIATION

Cannabis is an erect annual herb with a dioecious breeding system. Wild and cultivated forms of cannabis are morphologically variable, resulting in confusion and controversy over the taxonomic organization of the genus. Hilling [7] proposed 3 cannabis species, *C. sativa, C. indicia and C. ruderalis;* and 7 taxa based upon systematic speciation analysis of sample populations of 157 Cannabis accessions of diverse geographic origin, noting 52 separate alleles from 17 gene loci. The sativa gene pool includes fiber/seed landraces from Europe, Asia Minor, and Central Asia, and ruderal populations from Eastern Europe. The *indica* gene pool includes fiber/seed landraces from eastern Asia, narrow-leafleted drug strains from southern Asia, Africa, and Latin America, wide-leafleted drug strains from Afghanistan and Pakistan, and feral populations from India and Nepal. The ruderal includes plant populations from Central Asia.

Cannabinoid content and composition is highly variable among cannabis plants. Those with high Δ^9-tetrahydrocannabinolic acid (THCA)/low-cannabidiolic acid (CBDA) chemotypes are termed marijuana, whereas those with a low- Δ^9-THCA/high-CBDA chemotype are termed hemp. There are large differences in the minor cannabinoid constituents within these basic chemotypes. Breeding of cannabis for use as a drug and medicine, as well as improved cultivation practices, has led to increased potency in the past several decades with median levels of Δ^9-THC in dried female flowers of 11% by dry weight; and levels in some plants exceeding 23%. This breeding effort, largely a covert activity by marijuana growers, has produced hundreds of strains that differ in cannabinoid and terpenoid composition, as well as appearance and growth characteristics. Patients

report medical marijuana strains differ in their therapeutic effects, although evidence for this is anecdotal.

GENETIC STRUCTURE

Cannabis has a diploid genome (2n = 20) with a karyotype composed of nine autosomes and a pair of sex chromosomes (X and Y). Female plants are homogametic (XX) and males heterogametic (XY) with sex determination controlled by an X-to-autosome balance system. The estimated size of the haploid genome is 818 Mb for female plants and 843 Mb for male plants, owing to the larger size of the Y chromosome.

THE ENDOCANABOID SYSTEM

The important finding that Δ^9-THC was largely responsible for the psychotropic effects of cannabis prompted later research efforts that led to the discovery of the plant cannabinoids action through two types of cannabinoid receptor termed CB_1 and CB_2. Δ^9-THC and other compounds were found to target either or both of these receptors as agonists or antagonists both with important therapeutic applications. Later studies led to the elucidation of the capacity of mammalian tissues to synthesize and release endogenous cannabinoid receptor agonists. Two endocannabinoid agonists, arachidonoylethanolamide (anandamide) and 2-arachidonoylglycerol, are expressed in a manner that appears to maintain homeostasis within the central nervous system (CNS) to oppose, mediate or evoke a given effect. It is now known that CB_1 receptors are situated not only in the CNS but in many peripheral organs including immune cells, spleen, adrenals, autonomic ganglia, the heart, lungs, urogenital and gastrointestinal tracts. Activation of the CB_1 receptor, but not CB_2 evokes the well-known psychotropic effects of cannabis.

There are a wide variety of interactions between the CB_1 receptor system and other neurotransmitters and neuromodulators in the CNS, and peripheral nervous (PNS), and autonomic nervous system (ANS). Activation of CB_1 receptors evokes a retrograde inhibition of the neuronal release of

acetylcholine, dopamine, gamma amino-butyric acid, histamine, serotonin, glutamate, D-aspartate, glycine, and noradrenaline. These complex interactions are a testimony to the large number of physiological actions of cannabinoids, and their pharmacologic impact on the human body.

ENDOCANNABINOID SUBSTANCES

Δ^9-THC has the appearance of a sticky liquid crystal when warmed and a glass-like solid when cooled. It is the primary psychotropic constituent of marijuana. Like anandamide, it binds to CB_1 and CB_2 receptor initiating CNS and peripheral immunologic and autonomic physiological changes. Synthetic medications containing THC include Sativex®, Dronabinol, Marinol®, and Nabilone. Their pharmacologic agents have been approved by the FDA to treat a large number of conditions including chemotherapy and acquired immune deficiency syndrome (AIDS)-related anorexia/cachexia, nausea and vomiting, diverse inflammatory conditions, as well as post-traumatic stress disorder (PTSD). Plant-based THC content varies by cannabis strain and preparation. Devoid of its carboxyl group, THC, becomes psychoactive with a potency that decreases over time.

Recognition that some of the pharmacologic effects of cannabis preparations were attributed to the actions of cannabinoids other than THC led to the identification of other endocannabinoids. After Δ^9-THC, cannabidiol (CBD) occurs in the next highest concentration in strains of cannabis, and possesses equally potent antiemetic, neuroprotective, and anti-inflammatory properties, through complex interactions with the CB_1 receptor, THC's effects by increasing CB_1 receptor density or through other CB_1 receptor-related mechanisms. Cannabidiol extends the duration of the effects of THC via inhibition of the cytochrome P450, CYP3A and CYP2C enzymes, and activation of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors. And although devoid of psychoactive features, its psychotherapeutic influence stems from its ability to suppress the enzyme fatty acid amide hydrolase that metabolizes

anandamide, thus maintaining it at higher concentrations for a longer duration of time.

In 2008, β-caryophyllene (BCP) was shown to be selective CB_2 agonist exerting significant cannabimimetic anti-inflammatory effects in mice [8]. Whether this compound is able to modulate inflammatory processes in humans via the endocannabinoid system is not yet unknown. Caryophyllene does not bind to CB_1 receptors and therefore does not exert psychoactive effects. However, phytocannabinoid-terpenoid interactions that could produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections have been found. Non-cannabinoid plant components and putative antidotes to intoxicating effects of Δ^9-THC that could increase its therapeutic index have been noted.

PHARMACOKINETICS

The unique pharmacological properties of cannabis are due to the presence of cannabinoids, a group of more than 100 natural products that mainly accumulate in female flowers ("buds"). Tetrahydrocannabinol is the principle psychoactive cannabinoid and the compound responsible for the analgesic, antiemetic and appetite-stimulating effects of cannabis. Non-psychoactive cannabinoids such as CBD, cannabichromene (CBC) and Δ^9-tetrahydrocannabivarin (THCV), which possess diverse pharmacological activities, are also present in some varieties or strains [9]. Cannabinoids are synthesized as carboxylic acids and upon heating or smoking, decarboxylate to their neutral forms. For example, Δ^9-THCA is converted to THC. Although cannabinoid biosynthesis is not understood at the biochemical or genetic level, several key enzymes have been identified including a candidate polyketide synthase and the two oxidocyclases, THCA synthase (THCAS) and CBDA synthase, which form the major cannabinoid acids [10, 11]. To date, most pharmacokinetic studies of cannabinoids have focused on the bioavailability of inhaled Δ^9-THC, which varies substantially in the literature, likely due to differences in factors such as breath-hold length,

source of cannabis material, and method of inhalation [12]. In general, 25% – 27% of the THC is available for the systemic circulation after smoking. The latency of effect onset for inhaled cannabis is shorter than that of cannabis consumed orally, requiring only minutes from the time of consumption to see observable changes, compared to hours when taken by the oral route. Furthermore, cannabis taken orally results in lower peak THC levels in the blood, but effects are observed for a longer period of time. Hepatic cytochrome p450 enzymes govern cannabinoid bioavailability. THC is metabolized primarily by CYP 2C9, 2C19, and drugs that inhibit these enzymes, including proton pump inhibitors, protease drug inhibitors, macrolides, anti-mycotics, calcium antagonists, and some antidepressants, which can increase the bioavailability of Δ^9-THC. Conversely, drugs that potentiate hepatic enzymes responsible for metabolism of Δ^9-THC can lower its bioavailability including phenobarbital, phenytoin, troglitazone, and St. John's wort.

PRESCRIBING PRINCIPLES

The recommendation of a specific medical cannabis strain for various ailments is lacking. That decision is often determined by a number of factors, including financial concerns, potential risk to the patient, and specific goals of the patient. Some important contributing factors include medical history, cannabis use history, and financial barriers. Once all of these concerns have been addressed, a strain is selected by the clinician from a range of varieties recommended for medical use by authorized licensed producers. Each licensed producer produces different strains suitable for various medical purposes. Using the principles of "start low, go slow" titration, individuals with little or no experience, histories of bipolar disorder, strong familial schizophrenia, and/or a history of substance abuse begin their process with medical cannabis on a CBD-dominant strain. Patients with a history of cannabis use and no significant risk factors may initially be prescribed a strain with higher THC content and maximal CBD content. If a given patient fails to get relief from their initial strain, an increase in the Δ^9-THC content

may be recommended in a stepwise fashion, so long as serious risk factors are not present. If risk factors are present, the risk–benefit analysis for this patient must be readdressed.

Two FDA-approved cannabinoid drugs available for prescription in the US, Dronabinol, a synthetic THC compound, and Nabilone, a semisynthetic analog of THC with an approximately 10 times greater potency than Dronabinol. Both are approved for chemotherapy-associated nausea and vomiting, while Dronabinol is also approved for human immune deficiency (HIV)-associated anorexia. While both drugs have shown some efficacy as an adjuvant analgesic, the sedating and psychotropic properties of both agents limit their utility.

Nabiximols is an oral spray that is an approximately racemic mixture of THC and CBD, is approved for opioid-resistant, treatment-refractory cancer pain and MS-associated spasticity and central pain, and in the United Kingdom, Spain, and New Zealand, for MS-associated spasticity. It is a useful add-on analgesic for patients with opioid-refractory cancer pain at low and medium doses.

ROUTES OF ADMINISTRATION

Many patients have concerns about medical cannabis smoke, which contains many of the same carcinogenic chemicals as tobacco smoke. Ultimately, the optimal route of administration depends largely upon the desires and capabilities of the patient.

Inhalation by vaporization is the most effective route for deliverance of the medicinal cannabinoid content of medical cannabis. Both dried and extracted medical cannabis can be used in a vaporizer. Loading a vaporizer requires some degree of dexterity which may be limited in certain populations of patients, such as those with neurological and musculoskeletal impairments. Some patients note that there is temperature related vaporization of the administered drug, requiring extensive education in the use of a vaporizer

Oral ingestion of medical cannabis refers to consumption of cannabis oils or edibles. These are generally produced by infusing a lipophilic substance, like an oil or butter, with cannabis, which is then used in drops or in food. A number of recipes have become available online for the use of cannabis oil and butter in food, though some patients dislike the strong flavor. For patients with respiratory illnesses, the oral route is preferable. This method is limited, however, by lower absorption and bioavailability than for inhaled cannabis. Another potential concern is a lack of research on the effectiveness and safety of orally consumed cannabis for pain conditions. Given the increased latency of effect onset from orally consumed medical cannabis, patients should be cautioned to wait an adequate amount of time to feel the effects of the cannabis before readministering. While issues of dosing and effectiveness exist for orally administered cannabis, it is typically well tolerated by patients.

Sublingual tinctures are another, less common, route of administration for medical cannabis. Typically, these tinctures are extracted with ethanol, but vinegars and glycerin may also be used. The extracts are dropped under the tongue and held for a period of time sufficient to permit absorption by the branches of the lingual artery, including the sublingual and deep lingual arteries. If used properly, onset of action and bioavailability may be faster and higher for this route compared with oral administration, as is often observed with other drugs. Tinctures may be a favorable option in the future, as they mitigate the dosing and bioavailability issues associated with orally ingested cannabis and eliminate issues of tolerability with inhaled cannabis. However, the use of tinctures is not widespread today, and evidence supporting the therapeutic use of tinctures is limited. Moreover, patients often complain of the taste. In Canada, there is currently a sublingual cannabinoid pharmaceutical known as Sativex®. This is approved for multiple sclerosis (MS)-related neuropathic pain or spasticity, and for cancer-related pain and fibromyalgia. Alternative routes of administration include transdermal ointments and balms, ophthalmic drops, and rectal suppositories. While rarely used, all of these routes may have therapeutic potential for patients, though little research has been done to assess this likelihood.

EFFICACY

Studies of cannabinoid efficacy differ with some testing whole leaf marijuana, and others specific/isolated phytocannabinoids such as Δ^9-THC, or the cannabinoid combinations of nabiximols in a 1:1 ratio of THC: CBD compound, and others, synthesized compounds such as Nabilone. This heterogeneity makes meta-analysis more complicated and adds to the complexity of drawing clinical inferences of efficacy.

Efficacy of cannabinoids has been extensively reviewed in several recent meta-analyses. In a Cochrane-style meta-analysis, Whiting and colleagues [13] assessed the quality of the evidence assessing the effectiveness of cannabinoids in the treatment of nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity from MS, depression, anxiety, sleep problems, psychosis, glaucoma, and Tourette's syndrome, among a total of 79 randomized controlled trials (RCT) enrolling 6462 patients. Belendiuk and coworkers [14] assessed common state-approved medical and psychiatric indications for cannabinoids including Alzheimer's disease, amyotrophic lateral sclerosis, cachexia, cancer, Crohn's/inflammatory bowel disease, epilepsy, severe/chronic pain, glaucoma, hepatitis C, HIV/AIDS, MS, and post-traumatic stress disorder, noting the need for a significant amount of rigorous research to definitively ascertain the implications of isolated cannabinoids (THC, CBD) as well as species of smoked marijuana (*indica* and *sativa*) for these disorders. Koppel and colleagues [15] on behalf of the American Academy of Neurology (AAN) concluded that cannabinoids, particularly nabiximols, yielded benefit in patients with MS for spasticity, central pain or painful spasms, and urinary dysfunction. Friedman and Devinsky [16] provided a scholarly summary of the evidence for treatment of epilepsy with cannabinoids. While acknowledging pre-clinical and preliminary/anecdotal clinical data, they emphasize the importance of standard double-blind trials to help improve the state of knowledge.

Contraindications and Side Effects

There are only a few relative contraindications to the use of medical cannabis. Two such ones are frank psychosis or bipolar disorder, in which the use of strains with minimal or no THC content are recommended [17]. C. sativa allergy is noted in about 8% of the general population, although the incidence may be higher among individuals who identify as users of cannabis. Avoidance is recommended for patients with cannabis allergies to avoid potentially lethal anaphylaxis. However, mild rhino-conjunctivitis symptoms can be treated with antihistamines, intranasal steroids, and nasal decongestants. Immunotherapy has been used to treat cannabis allergies, however it is not yet common practice [18].

PATIENT CARE

When introducing a patient to medical cannabis for the first time, it is important to schedule frequent follow-ups until a strain has been selected that meets the treatment goals of both patient and physician. Since this process may require changes such as route of administration, an active follow-up schedule may be required to provide the patient with adequate knowledge to continue safely and confidently. Once a patient has been stabilized, follow-up visits should focus on monitoring for adverse reactions, including dependence. Medical document is necessary to allow a patient access to cannabis. The timing of a patient's follow-ups is an important medicolegal and health concern.

THE EMERGING MARIJUANA INDUSTRY

The challenge for the emerging marijuana industry is to raise standards and promote patient and physician satisfaction. Up until now, there has

been inconsistent evidence that the industry has made efforts to conduct quality assurance activities. Some dispensaries promise that they measure and warrant the chemical composition of each batch of their products. A reasonable generalization regarding the current state of affairs, however, is that the cannabis that patients purchase at the local cooperative will likely contain uncertain concentrations of THC/CBD and other compounds, despite what the label says. A study of 75 products randomly purchased from internet-listed dispensaries in San Francisco, Los Angeles, and Seattle showed accurate labeling of THC/CBD content in only 17% [19]. The majority (60%) were over-labeled, (at least 10% less cannabinoid content than claimed), while 23% were under-labeled (at least 10% more cannabinoid content than labeled). This fact raises a host of other considerations, including basic safety (might there be the presence of adulterants, congeners, contaminants, insecticides), dose-related concerns (little or no pharmacologic effect at one end and drug-related toxicities at the other), and potentially differing pharmacologic effects from batch to batch, just to name a few. It also adds an additional level of uncertainty to any efforts by the clinician to consider/discuss/counsel patients about dose, drug–drug interactions, and other routine clinical issues that might arise around the prescription or endorsement of a new treatment.

Increasing physician comfort in signing endorsements, attestations, or certifications of the possible efficacy of medical marijuana for a particular problem or symptom is an important goal for the marijuana industry. Equally vital is attracting physicians to perform case reviews and to complete the attestation paperwork that allows patients to purchase a medical marijuana ID card, which will then allow their patients to gain admittance and to purchase from a certified dispensary. By reducing the uncertainty about whether the chemical composition of what patients believe they are purchasing is in fact that which they are being sold will allow ordering physicians to give standard, informed medical advice.

CONCLUSION

Some physicians who care for patients with chronic illnesses and associated significant symptom burden take a "don't ask, don't tell" position regarding medical marijuana. Despite its convenience and tidiness, this is an increasingly untenable position. Medical marijuana and cannabinoid pharmaceuticals seem to be here for the duration; and there is a credible evidence base for their efficacy. They are now widely available and in widespread use. Moreover, conventional approved treatments to chronic illness are imperfect, and patients and families are often desperate to find alternatives. A widely recommended approach for physician endorsement of cannabinoid therapy begins with documenting a medical condition for which there is adequate proof that cannabis has efficacy and that a patient has failed first- and second-line non-cannabinoid pharmacotherapy. Such patients should be offered an FDA-approved cannabinoid (Dronabinol or Nabilone) and be free of known substance abuse and psychotic illness, and reside in a state where medical marijuana is legal. As cannabinoids ascend to first-line treatment for certain illness for symptoms management or other efforts to improve disease-related quality of life, physicians and patients will need to explore more effective ways of ensuring the safety and satisfaction of cannabinoid preparations.

There is emerging or well-established clinical evidence of the utility of medical cannabis in a variety of neurological disorders that have typically been refractory to conventional medications including epilepsy, dementia, multiple sclerosis, neuropathic pain, and headache. The endocannabinoid system has broad and overlapping functions that makes it uniquely suited to restore nervous system functions to homeostatic balance through modulating neuroimmunologic and neuroinflammatory responses and signaling in the brain. Δ^9-THC, the main bioactive plant cannabinoid, is available as a prescription medication and approved for treatment of cancer chemotherapy-induced nausea and vomiting, and cancer-related pain where they are synergistic with opioid analgesics. Cannabinoids have a favorable drug safety profile, but their medical use is predominantly limited by their psychoactive effects and their limited bioavailability.

THE CANNABIS PLANT

PHYTOCANNABINOIDS

Solymosi and Köfalv [20] have reviewed the active compounds of the cannabis plant. It is comprised of more than 500 known compounds [21] in addition to phytocannabinoids, including various alkanes, sugars, nitrogenous and flavonoid compounds, non-cannabinoid phenols, phenylpropanoids, steroids, fatty acids, β caryophyllene, and di- and triterpenes. Terpenes, β-caryophyllene and its oxidation products, give cannabis its characteristic odor, and are used in training dogs to confiscate hashish and marijuana. However they are highly volatile substances that are present in only fresh material.

With a C21 terpenophenolic compound structure and physiological and psychotogenic effects, there are more than 100 phytocannabinoids, classified into several major categories, each with representative molecules, including THC, CBN, CBG, CBC, and CBD, and differing isomers, biogenic precursors, acids, degradation products and artifacts. Phytocannabinoids are synthesized and accumulated as phytocannabinoid acids, for example, CBDA and THCA with higher concentrations in fresh plants. The latter is detectable in people who smoke or otherwise consume cannabis. There is a positive interactive effect of CBD on THC such that its

combined use reduces the adverse psychotogenic effects of Δ^9-THC while increasing its clinical efficacy and prolonging its duration [22]. The effects of extracted phytocannabinoids given as single-molecule pharmaceuticals differ from those of the crude drugs (marijuana, hashish) highlighting the importance of the highly complex interactions of the natural constituents present in the plant. The Δ^9-THC content of drug-grade cannabis leaves is more or less constant during development, while that of the bracts increases considerably during flowering [23]. Phytocannabinoid production is influenced by the specific cultivation protocol employed, and by environmental stressors such as humidity or drought, temperature, soil nutrient content, and illumination. Stress, which also causes the plant to grow smaller, is not necessarily associated with an overall reduced phytocannabinoid production the relative ratio of Δ^9-THC/CBD varies among the different cannabis species, strains and hybrids.

IDENTIFICATION OF CANNABIS

The identification of cannabis plants and products may be done on the basis of observation of general plant morphology, that is, the typical shape and venation of leaves and or by its unique chemical fingerprint by several analytical methods such as high-performance liquid chromatography, gas-liquid chromatography, or gas chromatography coupled with flame ionization or mass spectroscopy (IF). However, this is not always possible in case of forensic samples and different cannabis products. With the exception of hashish oil and other extracts, the characteristic trichrome of the cannabis plants on the surface of the fruiting and the flowering top may be microscopically identified. Phytocannabinoids provide a unique chemical fingerprint for cannabis identification and can be unequivocally identified by several analytical methods such as high performance liquid chromatography (HPLC), gas-liquid chromatography (GLC) or gas chromatography (GC) coupled with flame ionization or mass spectrometric (MS) detection [24-26]. In addition to discrimination between the different cannabis species, cultivars, chemovariants and samples collected by forensic

scientists on the basis of their phytocannabinoid composition can provide more precise information about indoor or outdoor plant cultivation, and even the country of origin. For chromatographic analyses, dried plant material is usually incubated for 1 to 4 hours with petroleum ether, chloroform, and hexane, methanol, and various other solvents. DNA-based profiling techniques used for cannabis identification use polymorphisms of the enzyme responsible for Δ^9-THCA synthesis. Fluorescent duplex-polymerase chain reactivity (PCR), and single nucleotide polymorphism assays to discriminate between drug-type and fiber-type cannabis. A candidate gene involved in phytocannabinoid biosynthesis distinguishes these two chemotypes [27]. [1]H-nuclear magnetic resonance spectroscopy is a promising non-destructive, fast and sensitive method to identify chemotypes during the entire cultivation period.

PHYTOCANNABINOIDS BIOSYNTHESIS

Cannabis plants accumulate cannabinoids as carboxylic acids in the secretory cavity of glandular trichrome. The most common cannabinoids, those with pentyl side chains, are CBD), Δ^9-THC, CBC and CBG. The biosynthesis of phytocannabinoids was first reported in 1965 [28] and is summarized in Figure 1. The first specific step in the pentyl cannabinoid biosynthesis is the condensation of the terpenoid moiety geranyl pyrophosphate (GPP) with the phenolic moiety olivetolic acid (OA; 5-pentyl resorcinolic acid) into CBG. This reaction is catalyzed by the enzyme geranyl pyrophosphate: olivetolate geranyl transferase (GOT; precursors for GPP are isopentenyl pyrophosphate (IPP) and dimethyl allyl pyrophosphate (DMAPP). These can originate from the mevalonate pathway (MVA) that is located in the cytoplasm and the deoxyxylulose pathway (DOX) that operates in the plastid compartments. The GPP incorporated into cannabinoids is derived via the DOX pathway of the glandular trichrome plastids. The phenolic moiety OA is generated by a polyketide-type mechanism. N-hexanoyl-CoA and three molecules of malonyl-CoA condense to a C12 polyketide, which is subsequently converted into OA by

a polyketide synthase. The condensation of n-hexanoyl-CoA and two, instead of three, molecules of malonyl-CoA, results in a C10 polyketide. This is subsequently cyclized into divarinic acid (DA; 5-propyl resorcinolic acid) by a polyketide synthase. Cannabinoids with propyl side chains result if GPP condenses with DA, into cannabigerovarin (CBGV). CBG is the precursor for THC, CBD and CBC. For each CBG conversion an enzyme has been identified: THC acid synthase, CBD acid synthase, and CBC acid synthase. These enzymes are not selective for the length of the alkyl side chain and convert CBGV into the propyl homologues of CBD, THC and CBC, which are indicated as cannabidivarin (CBDV), tetrahydrocannabivarin (THCV) and cannabichromevarin (CBCV), respectively. The total cannabinoid content as a polygenic character, is heavily affected by the environment and shows a Gaussian distribution within the progenies described so far. The cannabinoid composition shows discrete distributions in segregating progenies and is under mono or oligogenic control.

The qualitative and quantitative aspects of phytocannabinoid production is influenced by genes involved in phytocannabinoid production and to a lesser extent environmental factors as well as the growth and development of phytocannabinoid producing structures such as the secretory glands. Modification of the THC content of cannabis may be bred by disruption of phytocannabinoid biosynthesis or gland development. It has long been known that plants lacking glandular trichrome and plants carrying trichrome with white heads contain no cannabinoids and those with transparent trichrome and heads in the yellow–orange to brown color range to be rich in cannabinoids. There are examples of undetectable cannabinoids in certain strain of plants, however the genetic mechanism underlying the cannabinoid-free chemotype has been lacking. Until recently, cannabinoid composition was not considered independently and genetically distinct from the total cannabinoid content. Two physiological conditions could make a plant cannabinoid-free: a disrupted morphogenesis of glandular trichromes that are essential structures for cannabinoid synthesis, and a blockage of one or more biochemical pathways crucial for the formation of precursors upstream of CBG. The first condition would seriously affect the synthesis of

all other secondary metabolites that are produced largely or uniquely in the glandular trichrome. The second condition would affect metabolites other than cannabinoids, as in the case of an obstruction of the basic pathways of common precursors for different classes of end products.

De Meijer and colleagues [29] studied the inheritance of chemical phenotypes producing cannabinoid-free Cannabis sativa demonstrating that a cross between a cannabinoid-free plant and a high cannabinoid content plant yielded an F1 with low cannabinoid content. Inbred, the F1s produced F2s that segregated into the discrete chemotypes, 'cannabinoid-free', 'low content' and 'high content' in a 1:2:1 monogenic ratio. This tripartite segregation presented in binary form, with the chemotypes 'cannabinoids absent' and 'cannabinoids present' appearing in a 1:3 ratio. Inbred offspring from cannabinoid-free plants invariably remained cannabinoid-free. These results were explained by postulating a single allelic locus with a common functional allele that allowed cannabinoid synthesis and a rare null- or knockout allele that obstructed it. In explaining the morphological and biochemical effects of this knockout factor the authors concluded that cannabinoid-free segregants resulted from back-crosses with high content drug clones that had stalked glandular trichrome in normal densities, but the trichrome heads were dull and much smaller than those of their high cannabinoid content sister plants. Nevertheless, the trichrome of cannabinoid-free segregants appeared to be functional metabolic organs. Chemical comparison of contrasting segregant bulks did not reveal large differences in the content and composition of volatile terpenes, the production of which required functional trichrome. The absence of cannabinoids was probably the cause of the small trichrome heads, rather than being a result of them. The bracts and bracteoles of low content plants were microscopically almost indistinguishable from the cannabinoid-free plants except that they showed an occasional small but bright trichrome head. In these plants the small amount of cannabinoids appeared to be concentrated in just a few inflated trichrome and not evenly distributed throughout. Thus, the absence of cannabinoids was biochemically due to the blockage of one or more pathways crucial to the formation of precursors

upstream of CBG with the most plausible hypothesis, a blockage in the polyketide pathway towards the phenolic moieties OA and DA.

GLANDULAR SECRETORY STRUCTURES

The cannabis plant is comprised of several structures, many of which can be found on any ordinary flowering species. Cannabis grows on long thin stems with large leaves that fan out from structures called nodes. Clusters of buds, or colas, can be seen growing tightly together along the budding sites of lower branches while the main cola, sometimes called the apical bud, forms at the very top of the plant. Pistils contain the reproductive parts of a flower from which hair-like strands termed stigmas collect male pollen. The stigmas of the pistil begin with a white coloration and progressively darken to yellow, orange, red, and brown over the course of the plant's maturation.

A bract encapsulates the female's reproductive parts. Appearing as green tear-shaped leaves heavily covered in resin glands that produce the highest concentration of cannabinoids of all plant parts. Enclosed by these bracts and imperceptible to the naked eye, is the calyx, which is a translucent resin layer secreted through translucent, mushroom-shaped glands present on the leaves, stems, and calyxes. Trichomes, which originally served as protection against predators and the elements, are clear bulbous globes that ooze aromatic oils called terpenes as well as therapeutic cannabinoids like THC and CBD. The simultaneous presence of bear claw-shaped cystolithic trichomes on the adaxial leaf surface, and slender, non-cystolithic trichomes on the abaxial leaf surface are features used for forensic identification of cannabis. The number, size and distribution of different trichomes on the central leaflets of the compound leaves may be used to distinguish the major Cannabis taxa (i.e., *C. indica, C. ruderalis, C. sativa*) even before flowering stage.
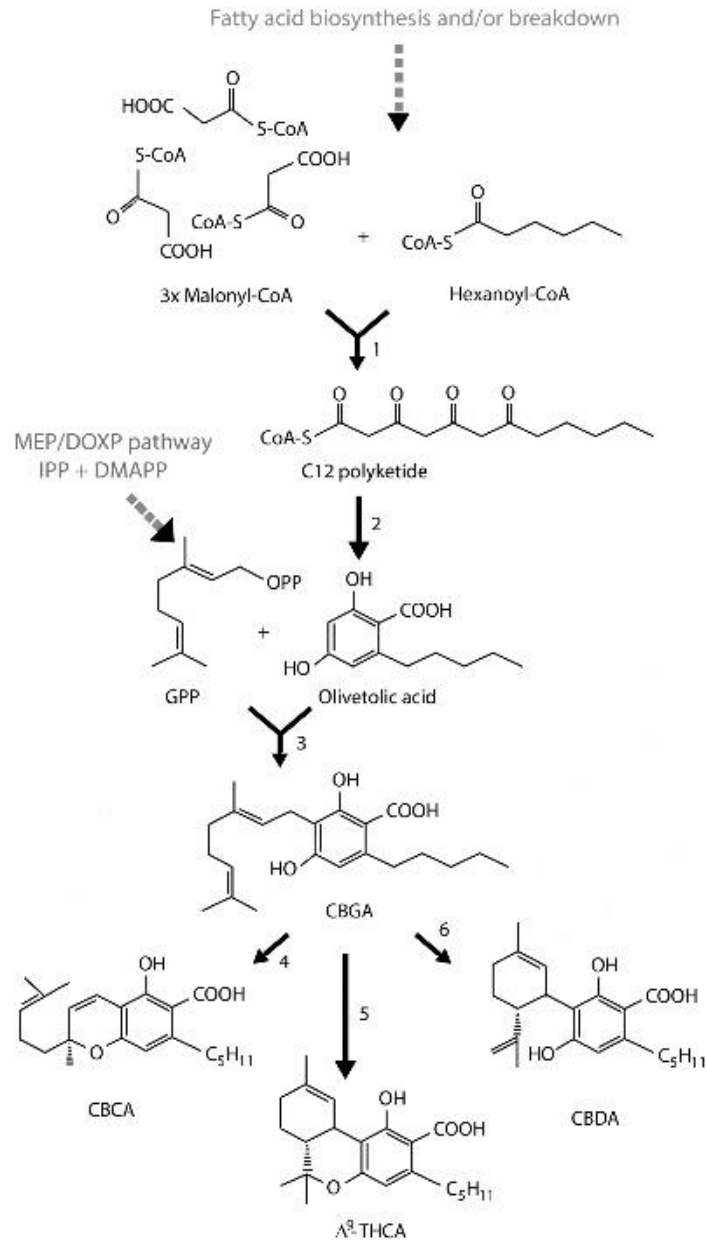
Figure 1. Biosynthetic pathway of the major phytocannabinoids. Reproduced from [30] with permission.

Three types of glandular trichomes can be distinguished on cannabis plants (Figure 2) [31] including small bulbous and large capitate-sessile glandular hairs, and large capitate-stalked trichomes with very high phytocannabinoid content (approximately 20 times higher content than those of capitate-sessile glands) that develop predominantly on the floral bracts and bracteoles after flower initiation [32-34]. The glands have a flattened-disc-like head composed of few to many cells and covered by the secretory product accumulated beneath a cuticular sheath.

The full-sized bulbous glands are 25-30 μm high and have a short stalk (stipe) and a head with 20 μm diameter. These heads contain 1, 2 or 4 secretory cells in a single layer, and their stalk is composed of 1 or 2 cells, bearing a 1- or 2-celled base layer. Mature capitate-sessile glands have very short axes consisting of one base and one stalk cell layer appearing to be attached directly to the bract surface with a larger circular long head containing 8 to 13 secretory cells arranged in a single layer 40 to 70 μm in diameter. Some authors distinguished two types of capitate-sessile trichomes based on their size: big ones present only in the flowers and smaller ones present also on the plant leaves and stems [32]. Capitate-sessile glands or capitate-stalked glands are the most conspicuous in young or old bracts, respectively.
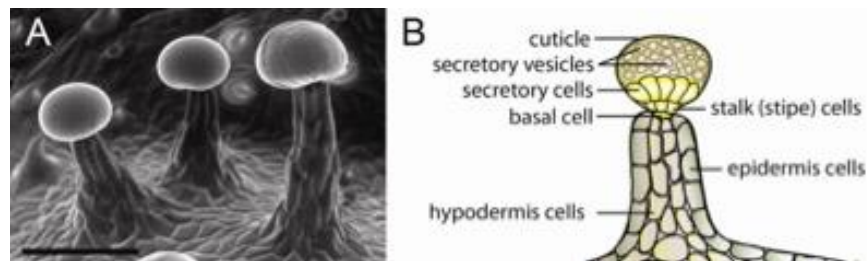
Figure 2. Scanning electronic micrographs of three capitate-stalked secretory glands on the abaxial epidermis of a perigonal bract surrounding the pistil in a drug-type of *Cannabis sativa* strain plant. Reproduced from [30] with permission.
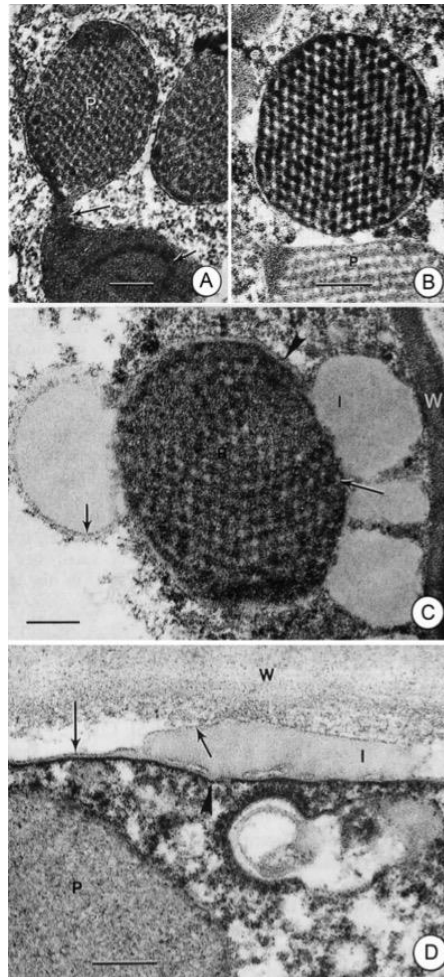
Abbreviations: P, plastid; R, reticulate body; W, cell wall. Reproduced from [35] with permission.

Figure 3. Transmission electron micrograph showing plastids and the secretory process in Cannabis sativa disc cells from conventionally chemically fixed samples. A. Plastid with constriction (long arrow) and two distended regions, the lower one containing a thylakoid (short arrow). B. Plastic section containing a reticulate body with different lattice orientations that fills the entire circular plastid section. C. Plastid with reticular body and voluminous inclusions containing the secreted material along the envelope surface (arrowhead). D. Plasma membrane (long arrow) showing inclusion positioned in periplasmic space delimited by a surface (short arrow) and being in contact with the plasma membrane (arrowhead).

PRODUCTION AND ANALYSIS OF GLANDULAR TRICHOME PHYTOCANNABINOIDS

Trichomes, especially the capitate-stalked glandular hairs, are well known as the main sites of cannabinoid and essential oil production of Cannabis *sativa*. Cannabis plastids as seen in transmission electron microscopy (EM) (Figure 3) [35] possess lobulated and dilated features subserving a function, other than photosynthesis, of the synthesis and secretion of phytocannabinoids. Interestingly, Δ^9-THCA synthase enzyme activity has been found in the non-cellular secretory cavity of glandular trichomes, indicating that this enzyme may also be secreted out along with other compounds to the cavity, and that the biosynthesis of THCA also terminates extracellularly [36]. The secretion and transport of synthesized phytocannabinoids and their precursors, and the synthetic enzymes, into the secretory cavity were investigated by Happyana and colleagues [37]. Cannabinoids were analyzed in extracts of collected cells of capitate-sessile and capitate stalked trichomes of 8-week old plants showing THCA, CBDA, and CBGA as the most-abundant compounds in all analyzed samples while their decarboxylated derivatives, THC, CBD, and CBG, co-detected in all samples, were present at significantly lower levels; CBC along with CBN were identified as minor compounds. The detection of metabolites in the stems of capitate-stalked trichomes indicates a complex biosynthesis and localization over the trichome cells forming the glandular secretion unit.

Chapter 3

CANNABINOID NEUROPHARMACOLOGY

The cannabinoid system is ubiquitous in the animal kingdom, with multiple functions that aid an organism in maintaining equilibrium. These stabilizing effects include modulation of stress and pain, suggesting that manipulation of the endocabinoid system may have profound therapeutic potential for the management of diverse neurological disorders. The endocannabinoid system has three broad and overlapping functions in the human nervous system. The first is a stress recovery role, operating in a feedback loop in which endocannabinoid signaling is activated by stress and functions to return endocrine, nervous and behavioral systems to homeostatic balance. The second function is the regulation of energy balance through control of the intake, storage and utilization of nourishment. The third involves immune regulation in which endocannabinoid signaling activated by tissue injury, modulates immune and inflammatory responses.

In the nervous system, neurotransmission and neuroinflammation are mediated by the endocannabinoid signaling system [38]. The endocannabinoid system has emerged as one of the key regulatory mechanisms in the brain, controlling multiple events such as mood, pain perception, learning and memory, is thought to provide a neuroprotective role during traumatic brain injury and as part of the brain's natural compensatory repair mechanism during neurodegeneration [39]. This

autonomous signaling and neuromodulatory system is positioned to be involved in multiple physiological functions including antinociception, neurocognition and memory, neuroinflammation, and immune recognition.

Endocannabinoids are also key mediators of many aspects of human health and disease. The biological activity of one endocannabinoid, anandamide, depends on the metabolic control exerted by biosynthetic, catabolic and oxidative pathways working together. Cellular uptake and intracellular trafficking of anandamide are crucial steps in the process. Whereas the identity of anandamide transmembrane carriers remains undetermined, recent insights have been gained related to its intracellular stores in adiposomes, and intracellular binding proteins, particularly fatty acid binding proteins, albumin and heat shock protein (HSP)-70. On this basis, there has been a reconsideration of the dogma that endocannabinoids are exclusively synthesized and released 'on demand', and suggest that their metabolic control is complemented by intracellular trafficking and storage in specific reservoirs.

CANNABINOID AND ENDOCANNABINOID SYSTEMS

To date, two cannabinoid receptors have been identified by molecular cloning, namely, CB_1 and CB_2 receptors. The CB_1 receptors are expressed by the neurons and regulate the release of neurotransmitters, while CB_2 receptors are expressed by the microglia, regulating their motility and immunomodulator production [40]. Their nomenclature has been standardized [41]. Their cloning and initial characterization were achieved in the early 1990s [42, 43]. The high similarity in amino acid sequence of the 473 amino acid-long rat CB_1 and the 472 amino acid-long human CB_1 receptor (hCB_1R) is consistent with evolutionary conservation. CB_1 and CB_2 receptors modulate intracellular cation levels. The former is negatively coupled to N-, P- and Q-type voltage-gated Ca^{2+} channels, and positively associated with inwardly directed K^+ channels and intracellular Ca^{2+} current. The stimulation of CB_2 receptors can produce transient increases in intracellular Ca^{2+} concentration.

CB$_1$receptor expression and protein densities are highest in humans in areas of the limbic system namely, the cingulate gyrus, frontal, secondary somatosensory and motor cortices, hippocampus, and dorsolateral striatum, while moderate levels of CB$_1$receptor expression are found in the hypothalamus and ventral striatum/nucleus accumbens.

There is an emerging body of evidence supporting a physiological and pathological roles for neuronal CB$_2$receptors in the brain, notably in hippocampal principal neurons, where they modulate the sodium/bicarbonate co-transporter, thereby causing a hyperpolarization of neurons.

The phytocannabinoids or natural cannabinoids can be distinguished from endogenous chemical cannabinoid receptor ligands or endocannabinoids, and the synthetic non-selective and selective cannabinoid receptor agonists. The endogenous counterparts of Δ^9-THC, collectively termed endocannabinoids, include N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG). Considerable research has shed light on their impact on human health and disease, identifying an ensemble of proteins that bind, synthesize and degrade them, and that altogether form the endocannabinoid system.

Phytocannabinoids differ in their action at the two receptors [44]. In most assays, Δ^9-THC acts as a partial agonist at CB$_1$ and CB$_2$ receptors. A dose of 50 μg/kg is enough to elicit subjective responses in humans. Since THC has relatively low cannabinoid receptor efficacy, classical pharmacology predicts that its ability to activate these receptors will be particularly influenced by the density and coupling efficiencies of these receptors. Whereas downregulation of cannabinoid receptors may cause THC to produce antagonism rather than agonism, their upregulation is expected to enhance the ability of this partial agonist to activate cannabinoid receptors. In contrast to THC, CBD lacks detectable psychoactivity, and only displaces the selective agonist [3H]CP55940 from cannabinoid CB$_1$ and CB$_2$ receptors at concentrations in the micromolar range. Since it displays such low affinity for these receptors, much pharmacological research with CBD has been directed at seeking out and characterizing CB$_1$- and CB$_2$-independent modes of action for this phytocannabinoid. Evidence

has emerged that in spite of its low affinity for CB_1 and CB_2 receptors, CBD can interact with these receptors at reasonably low concentrations.

The two endocannabinoids, AEA and 2-AG, bind with different affinities to CB_1 and CB_2 receptor [45]. Precursors for both anandamide and 2-AG are believed to be stored in the cell membranes and released on demand for endocannabinoid signaling where the synthesis and the release of the two endocannabinoids occur with multiple synthetic pathways from its principal precursors. Activation of CB_1 is involved in the inhibition of excitatory and inhibitory neurotransmission and the modulation of cognitive, memory and motor functions, as well as analgesia, whereas CB_2 is mainly expressed by cells of the immune system where it is commonly associated with the regulation of different immune functions. The identification of CB_2 in brainstem neurons and its presence in activated microglial cells and astrocytes, or in certain subsets of neurons upon insult has led to increased scrutiny of its exact function. Up-regulation of CB_2 is associated with chronic inflammation of the nervous system. Activation of CB_1 and CB_2 trigger the signaling pathway of inhibition of adenylyl cyclase activity, with reduction of cAMP levels, and inactivation of protein kinase A. Both CB_1 and CB_2 also Other signaling pathways include coupling to ion channels (N- and P/Q-type Ca^{2+} channels and voltage-gated K^+ channels), activation of phospholipase-Cβ, and ceramide biosynthesis.

Many different regulatory actions have been attributed to endocannabinoids, and their involvement in several pathophysiological conditions is under intense scrutiny [46]. Both CB_1 and CB_2 receptors participate in the physiological modulation of many central and peripheral functions. The ability of the endocannabinoid system to control appetite, food intake and energy balance has recently received considerable attention, particularly in the light of the different modes of action underlying these functions. The endocannabinoid system modulates rewarding properties of food by acting at specific mesolimbic areas in the brain. In the hypothalamus, CB_1 receptors and endocannabinoids are integrated components of the networks controlling appetite and food intake. Interestingly, the endocannabinoid system was recently shown to control several metabolic functions by acting on peripheral tissues such as

adipocytes, hepatocytes, the gastrointestinal tract, the skeletal muscles and the endocrine pancreas.

Cannabinoids not only affect the activity of the principal glutamatergic cells and the GABAergic inhibitory neurons, but are also capable of modulating the release of other neuromodulators. This interaction is bidirectional, because endocannabinoid release can be triggered by the stimulation of neuromodulator receptors. Cannabinoid receptors form heterodimers with receptors of other neuromodulator systems at different levels for the fine-tuning of synaptic transmission and synaptic plasticity, a process that underlies learning and memory, emotions, stress coping, mood, motivation, reward, and cognition.

Adult neuronal stem cells contain CB_1 receptors [47], and cannabimimetics in most cases stimulate the proliferation of neural progenitors in the neurogenic niches. This attempts to provide the maturing and adult brain with a constant supply of new cells that migrate toward and integrate themselves in the circuitry where they are needed with major implications in learning and forgetting, mood disorders and stroke repair.

Chiurchiù and colleagues [48] reviewed endocannabinoid signaling in innate and adaptive immunity. Innate or in-born immunity comprises the cells and mechanisms that defend the host from infection. Collectively, it recognizes, and responds to pathogens in a generic way. However, unlike the adaptive immune system, innate immunity, is not long-lasting. By contrast, adaptive immunity is associated with immunological memory long after the initial encounter with a specific pathogen. It is associated with an enhanced response to subsequent encounters as for example in vaccination. The adaptive immune system includes both humoral immunity components (circulating antibodies and complement proteins) and cellular constituents (B-cells, $CD4^+$ T helper [$CD4^+$], cytotoxic [$CD8^+$], and natural killer [NK] T-cells).

The immunosuppressive effects of endocannabinoids on immune cells are primarily mediated through CB_2, whose expression is usually higher than that of CB_1. Unlike endocannabinoids and their metabolizing enzymes, the presence and distribution of CB_2 receptors within immune cells vary strongly and have been mainly investigated in human immune cell

populations. There is extensive information regarding the expression of CB receptors by the various blood immune cells of healthy human volunteers [49] reinforcing the view that the endocannabinoid system performs valuable signaling to support innate and adaptive immunity, and not just exerting either immunosuppressive or stimulatory effects on the immune system. Monocytes/macrophages are highly plastic, changing the functional phenotype depending on environmental cues. The cells reside in every tissue of the body, where are referred to as Kupffer cells in the liver, and microglia in the CNS. The CB_1 and CB_2 receptors are highly expressed in human monocytes/macrophages and microglial cells where their metabolism is modulated in response to inflammatory stimuli, so regulating the tone of the endocannabinoid system. There is limited information as to the role of neutrophils, mast cells, basophils and eosinophils in endocannabinoid system-related immunity. Evidence for an immunosuppressive role of endocannabinoids on T-cells surfaced shortly after isolation and purification of AEA, demonstrating its dose-dependent anti-proliferative effects on human T-cells [50]. Indeed, micromolar doses of AEA rapidly inhibited mitogen-induced DNA synthesis, and this was associated with induction of apoptotic cell death. Since then, interest was primarily focused on phytocannabinoids and synthetic agonists/antagonists selective for CB_1 or CB_2. It is recognized that AEA is a potent immunosuppressor of T-cell proliferation and cytokine release, acting mainly through CB_2. NK cells are a type of cytotoxic lymphocyte that provide rapid responses against virally infected cells and cancer cells. Surprisingly, NK cells have been shown to express both CB_1 and CB_2, and to release high levels of AEA and 2-AG [51]. In contrast, B-cells, which are involved in the production of antibodies against antigens, are capable of acting as antigen-presenting cells. Antibody-producing plasma cells are among the immune cells that express the highest levels of CB_2. It appears that CB_2 receptors may represent a novel pharmacological target for selective agonists designed to suppress autoreactive immune responses while avoiding CB_1 receptor-dependent psychoactive adverse effects. Thus, modulation of the endocannabinoid levels by specifically inhibiting their breakdown enzymes or by inducing

their production, may provide a new avenue of regulating the immune system.

The existence of intracellular AEA binding proteins and stores implies that the current dogma of endocannabinoid biology, that these compounds are synthesized and released exclusively on demand, should be reconsidered. It has been proposed that AEA intracellular binding proteins (AIBP) might act as AEA intracellular transporters that work together with adiposomes to make AEA available both for receptor activation, and for distinct metabolic pathways, away from the site and time of AEA biosynthesis [52]. Increased levels of AEA are observed in several human pathologies including inflammatory diseases. Yet it is becoming increasingly evident that the complex biological activity of AEA depends on its transport to distinct intracellular sites where metabolic and signaling pathways take place. It is suggested that lipid bodies or adiposomes may be acting as a platform for accumulation, trafficking, metabolism, and signaling of AEA. By acting as reservoirs, adiposomes could sequester AEA in a form that is not in free equilibrium with the extracellular pool. Such a sequestration might explain how the intracellular concentration of AEA can be up to three orders of magnitude higher than the external level, allowing the cells to concentrate AEA. Sequestration into adiposomes might also explain the AEA gradient needed to drive its influx, contributing to the uptake so far attributed only to membrane transporters. Acting not only as shuttles for AEA transporting adiposomes resemble lipoproteins, and characterized by a core of neutral lipids surrounded by polar lipids and specialized proteins, able to ferry between tissues ; adiposomes are associated with various AEA-metabolizing enzymes making them a starting point for different metabolic pathways. Lipid bodies seem to constitute an important site for the fate of AEA, dictating its sequestration, degradation or oxidation. Its storage in adiposomes may account for the improved half-life lasting long enough to trigger receptor activity, based upon the estimate for the sequence of peroxisome proliferator-activated receptors (PPAR)-dependent genomic events typically in the range of hours ; compared with classical non-genomic events associated with rapid activation (within minutes) of CB and transient receptor potential vanilloid-1 (TRPV1) receptors [52]. It should be expected

that cells have biochemical tools to ensure that the half-life of AEA spans from minutes to hours, and that the accumulation of AEA well above levels to reach the doses required for PPAR activation. Cells with more prominent adiposomic compartment such as adipocytes and macrophages, might use AEA, more as a classic hormone that as a local short-lived mediator. It is interesting to note that adipocyte differentiation, lipid and glucose metabolism, as well as inflammatory responses, are regulated by AEA and its congeners through PPARs. The molecular details that allow specificity of AEA targeting to its different intracellular sites remain incompletely understood. Future research will be focused on additional intracellular binding proteins and storage sites that ferry endocannabinoids other than AEA, and other player involved in endocannabinoid trafficking and accumulation for targeted drug development.

CANNABIS EFFECTS

The method of cannabis consumption directly affects its psychobiological response. Inhalation is the most typical mode of consumption. Oral ingestion delays the onset of effects by 0.5-2 hours, and the circulating levels of THC will be smaller but longer-lasting than when it is smoked. There is a delay in the appearance of subjective high after the plasma peak of Δ^9-THC levels. The CNS probably sequesters THC from the blood across the blood brain barrier (BBB) due to its high lipophilic content. Following a single administration of 10 mg of THC in a cigarette, levels rapidly drop below 1% of the original in 12 hours but this is only a crude estimation of its elimination kinetics. Among chronic marijuana subjects who smoked four cigarettes during a two day period, each containing 15 mg of deuterium-labelled Δ^1-THC, an elimination half-life in the blood plasma was found to be about 4 days [53].

The relation between marijuana consumption and the development of tolerance was investigated in volunteers who were given access to one-gram (2.1% THC) marijuana cigarettes during a 21-day smoking period [54]. Tolerance did not develop for the two most reliable indexes of marijuana

intoxication unless heavy doses of THC were repeatedly self-administered. The tendency to increase consumption during this time was not necessarily associated with the development of tolerance. In the West, where marijuana and relatively low dose THC content is widely smoked, dependence in the sense of drug-seeking behavior also appears to be less a function of any pharmacologic reinforcing properties the drug may have, than of secondary (conditioned) reinforcement derived from the social milieu in which the marijuana is smoked.

Approximately 9% of those who experiment with marijuana have a risk of addiction according to the criteria for dependence in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [DSM-IV]) [55]. The number goes up to about 1 in 6 among those who start using marijuana as teenagers and to 25 to 50% among those who smoke marijuana daily [56]. There is also recognition of a bona fide cannabis withdrawal syndrome [57] with symptoms that include irritability, sleeping difficulties, dysphoria, craving, and anxiety, all of which makes cessation difficult and contributes to relapse. Marijuana use by adolescents is particularly troublesome. Adolescents' increased vulnerability to adverse long-term outcomes from marijuana use is probably related to the fact that the brain, including the endocannabinoid system, undergoes active development during adolescence. As compared with persons who begin to use marijuana in adulthood, those who begin in adolescence are approximately 2 to 4 times as likely to have symptoms of cannabis dependence within 2 years after first use [58].

There are limited data regarding the relationship between cannabinoids and metabolic processes. However, among 4,657 adult men and women from the National Health and Nutrition Examination Survey assessed between 2005 and 2010 by a multivariable adjusted model, current marijuana use was associated with 16% lower fasting insulin levels and 17% lower homeostasis model assessment of insulin resistance [59]. There was also a significant association between marijuana use and smaller waist circumferences.

MEDICAL CANNABIS TAXONOMY

CHEMOTAXONOMY

With over a hundred different cannabinoids characterized, THC is considered the primary active ingredient responsible for its antiemetic, neuroprotectant, and anti-inflammatory properties as well as the ability to reduce certain forms of neuropathic and chronic pain, whereas CBD, endows medical cannabis products with neuroprotective, anti-inflammatory, and antiseizure properties without the intoxicating effects of THC. Other minor cannabinoids, such as CBG, CBC, and THCV, exhibit other interesting pharmacological properties. As cannabinoids are the major active ingredients found in cannabis, the resulting products can be categorized from a chemotaxonomic perspective according to cannabinoid levels for both medical and legal purposes. Small and Beckstead [60] identified three chemical types (chemotypes) based on ratios of THC and CBD. Type I contained high THC ($> 0.3\%$) and low CBD ($< 0.5\%$). Type II contained high THC ($> 0.3\%$) and high CBD ($> 0.5\%$). Type III had high CBD ($> 0.5\%$) and low THC ($< 0.3\%$). Hilling and Mahlberg [61] confirmed that a plant's dry-weight ratio of THC to CBD could be assigned to one of three chemotypes and that alleles B(D) and B(T) encoded alloenzymes that catalyze the conversion of cannabigerol to CBD and THC, respectively. The

investigators [61] further determined the frequency of B(D) and B(T) from CBD and THC banding patterns noting two biotypes (infraspecific taxa of unassigned rank) of *C. sativa* and four biotypes of *C. indica*. Mean THC levels and the frequency of B(T) were significantly higher in *C. indica* than *C. sativa*. The proportion of high THC/CBD chemotype plants in most accessions assigned to *C. sativa* was < 25% and in most accessions assigned to *C. indica* was > 25%. Plants with relatively high levels of tetrahydrocannabivarin (THCV) and/or cannabidivarin (CBDV) were common only in *C. indica.*

Studies on the inheritance of cannabinoid phenotypes have demonstrated that the chemotype can be independent from the plants morphology [62]. Drug type I cultivars have increased in potency containing upward of about 15 – 20% THC [63, 64], as have type II and type III cultivars [65-67]. Clinical research further demonstrates that the combination of THC and CBD alters its effects [68-70], indicating the importance of knowing the active compound ratios when using cannabis for medical purposes.

PHYSICAL CHARACTERISTICS

Medical cannabis users can discriminate between cannabis preparations based on a variety of physical characteristics. The supply of a standardized herbal cannabis product within a legal medical access program needs to be guided by user's feedback to ensure compliance. In early studies of the acceptance of herbal cannabis products acceptable to patients to maximize adherence to study protocols, Ware and colleagues [71] conducted a randomized controlled crossover trial of 4 different herbal cannabis preparations among 8 experienced and authorized cannabis users with chronic pain. Preparations were varied with respect to grind size, THC content and humidity. Subjects received each preparation on a separate day and prepared the drug in their usual way in a dedicated and licensed clinical facility. They were asked to evaluate the products based on several physical characteristics (smell, color, humidity, grind size, ease of preparation), and

overall appearance and smoking characteristics (burn rate, hotness, harshness and taste). Five-point Likert scores were assigned to each characteristic. An analysis of variance (ANOVA) for cross-over design was calculated to assess the comparison between products, demonstrating indeed, that physical characteristics were important to patients in their adherence to study protocols.

Terpenoids

Natural aromas are due to plant terpenoids, sometimes called isoprenoids. This large diverse class of naturally occurring organic chemicals similar to terpenes, derive from five-carbon isoprene units (Figure 4) that are assembled and modified in many different ways for their aromatic qualities.

Terpenoids also play a role in traditional herbal remedies where they contribute to the scent of eucalyptus, the flavors of cinnamon, cloves, and ginger, and the yellow color in sunflowers. Well-known terpenoids include citral, menthol, camphor, ginkgolide and bilobalide found in Ginkgo biloba, and of course, in cannabinoids from the three main types of cannabis plants, sativa, indica, and ruderalis. As already described, sativa plants are described as taller and loosely branched, whereas indica is typically shorter, more densely branched, and conical in shape. Ruderalis is described as short (≤ 2 feet) at maturity and sparsely, if at all, branched.
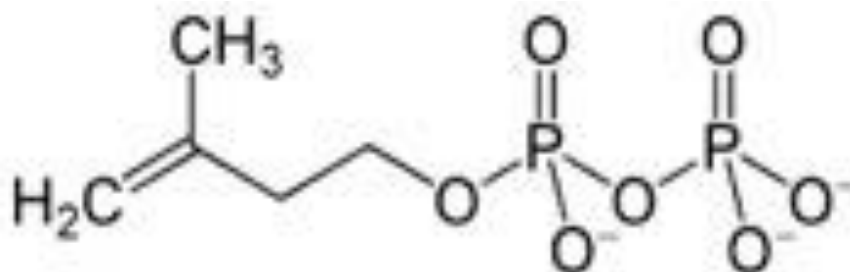
Figure 4. Chemical structure of the terpenoid.

Cannabis produces over 120 different terpenes [72]. While cannabinoids are odorless, terpenoids are responsible for the unique odor of cannabis, and each variety has a slightly different profile that can potentially be used as a tool for identification of different varieties or geographical origins of samples. They provide a unique and complex organoleptic profile for each variety that is appreciated by novice cannabis users and connoisseurs. In addition to many circulatory and muscular effects, some terpenes interact with neurological receptors. A few terpenes produced by cannabis plants also bind weakly to cannabinoid receptors. Some terpenes can alter the permeability of cell membranes and allow in either more or less THC, while other terpenes can affect serotonin and dopamine chemistry as neurotransmitters. Terpenoids are lipophilic, and can interact with lipid membranes, ion channels, a variety of different receptors (including both G-protein coupled odorant and neurotransmitter receptors), and enzymes. Some are capable of absorption through human skin and passing the BBB. Generally speaking, terpenes are considered to be pharmacologically relevant when present in concentrations of at least 0.05% in plant material [72, 73]. Thus, although there are an estimated 120 different terpenes, only a few are produced at high enough levels to be detectable, and fewer still which are able to reach pharmacologically relevant levels.

Seventeen of the most highly expressed terpenes include terpinolene, alpha phellandrene, beta ocimene, carene, limonene, gamma-terpinene, alpha pinene, alpha terpinene, beta pinene, fenchol, camphene, alpha terpineol, alpha humulene, beta caryophyllene, linalool, cary oxide, and myrcene. A survey of the terpene profiles of several cannabis varieties has found that these terpenes express at high enough levels so as to have their own pharmacological effects and also to act in synergy with cannabinoids. Both experts and consumers believe that there are biochemical and phenomenological differences between different varieties of cannabis, which are attributed to their unique relative cannabinoid and terpenoid ratios. This is known as the entourage effect and is generally considered to result in plants providing advantages over only using the natural products that are isolated from them [72].

Table 1.

TERPENE	BENEFIT	AROMA
Pinene Also found in pine needles	Anti-inflamatory Anti-bacterial Bronchodilator Aids memory	Pine Earth
Myrcene Also found in hops	Sedative Sleep aid Muscle relaxant	Flowers Pungent Earth
Limonene Also found in citrus	Treats acid reflux Anti-anxiety Antidepressant	Citrus Fresh spice
Terpinolene Also found in coriander	Analgesic Pain reduction Digestive aid Stomachic	Pine Herbal Anise Lime
Linalool Also found in lavender	Anesthetic Anti-convulsive Analgesic Anti-anxiety	Flowers Lavender Citrus Fresh spice
Terpineol Also found in mugwort	Calming aid Antibacterial Antiviral Immune system	Pleasant lilac Citrus Wood
Caryophyllene Also found in black pepper	Anti-inflammatory Analgesic Protects cells lining Digestive tract	Citrus Spice
Humulene Also found in basil	Anti-inflamatory	Robust Herbaceous Earth
Ocimene Also found in thyme and alfalfa	Decongestant Antiseptic Antiviral Bactrericidal	Citrusy green Wood Tropical fruit

Terpenoids can be extracted from the plant material by steam distillation yielding the essential oils, or by vaporization, however the yield varies

greatly by plant tissue, type of extraction, age of material, and other variables. Typically the yield of terpenoids in cannabis is less than 1% by weight on analysis; however it is thought that they may comprise up to 10% of the trichome content. Monoterpenoids are especially volatile, thus decreasing their yield relative to sesquiterpenoids [72]. Some of the most commonly found terpenoids in cannabis are summarized in Table 1, with their individual organoleptic properties as well as their basic pharmacology.

In a recent analysis of terpenoid chemotypes in medical cannabis sativa cultivars, Fischedick [74] studied terpenoid content of cannabis accessions from a single dispensary in California. Terpenoids were quantified by gas chromatography with flame ionization detection and peak identification was confirmed with gas chromatography mass spectrometry. Quantitative data from 16 major terpenoids were analyzed using hierarchical clustering analysis (HCA), principal component analysis (PCA), partial least squares discriminant analysis (PLS-DA), and orthogonal partial least squares discriminant analysis (OPLS-DA). Based on the HCA, the cultivar names could be broken down into five groups. First, a myrcene-dominant group made up of the Purple Cream, Grape Ape, Purple Princess, Blue Dream, Strawberry Haze, Godfather, and Purple Urkle cultivars. A second terpinolene-dominant group composed of the Jack Herer and Trainwreck Cultivars. Another third group composed of the cultivars named as Crown Og, Skywalker Og Kush, Og Kush, Gas, Tahoe Og Kush, Triple O, Gelato, and Miami White Kush dominated in myrcene and limonene. Distinguishing characteristics among these cultivars were the relatively higher levels of the monoterpenoid alcohols α-terpineol, endo-fenchyl-alcohol, and linalool. A fourth group of cultivars were dominated by β-caryophyllene, which included Blue Cookies, Girl Scout Cookies, Animal Cookies, Thin Mints, Fortune Cookies, Sherbert, Chemdog, and Gorilla Glue #4 (gorilla glue). A fifth group composed of Master Kush, Bubba Kush, Mr. Nice, and Sour Diesel tended to dominate in myrcene, limonene, or β-caryophyllene. The five groups were named myrcene (first), terpinolene (second), Og Kush (third), caryophyllene (fourth), and bisabolol (fifth), respectively. More sensitive methods for terpenoid analysis in cannabis samples have been described employing high- throughput homogenization to prepare sample

extract, which is then profiled for cannabinoids and terpenes by HPLC-diode array detector and GC-flame ionization detector, respectively [75]. Information about terpenoid chemotypes can allow doctors and clinical researchers to design studies to assess whether they have different medicinal or subjective effects, despite similar cannabinoid content. Since it is unlikely that the popularly used cultivar names ("strain" names as they are commonly referred to in the cannabis industry) will go away, the chemotype approach allows a more objective way of understanding cannabis chemical diversity for the newly emerging cannabis industry. Combining chemotaxonomic data, with morphological and genetic data, would provide a more complete picture of cannabis taxonomy.

CANNABIS PLANT CULTIVATION

As in other plants cultivated for pharmaceutical purposes, product development for medicinal cannabis entails careful cultivation and processing, beginning with the extraction of and purification of the active pharmaceutical agents. Achieving this, using raw cannabis as a feedstock, is especially challenging. The plant material is extremely inhomogeneous, and the ratios of active ingredients are affected by a range of factors including synergy of active ingredients, plant genetics, the induction and maintenance of flowering, achieving a mature cannabinoid profile at harvest, growing conditions, and the methods used to process and formulate the materials. It is only when optimal conditions are achieved in all of these factors that the medical cannabis agent will be both maximally medically effective and satisfying for the patient.

According to Potter [76] each mL of the prescription medicine which in the case of Sativex®, produced by GW Pharmaceuticals, contains 38-44 mg and 35-42 mg (as soft extracts) from *Cannabis sativa L. folium cum flore* (Cannabis left and flower) corresponding to 27 mg of THC and 25 mg of CBG. Among the other ingredients are naturally occurring cannabis-derived terpenoid ingredients, several of which are pharmacologically active.

Synergistic interactions are of vital importance in phytomedicines especially medical cannabis [72, 77]. Synergistic interactions explain both

the difficulty in isolating a single active ingredient, and the efficacy of apparently low doses of active constituents in an herbal product. The concept that a whole or partially purified extract of a plant offers advantages over a single isolated ingredient underpins the philosophy of many other herbal medicines. Four basic mechanisms of synergy have driven medical cannabis product development: (i) multi-target effects; (ii) pharmacokinetic effects such as improved solubility or bioavailability; (iii) agent interactions affecting resistance; and (iv) modulation of adverse events. The development of a new generation of phytopharmaceuticals will emerge as they are incorporated into regimens of other naturally occurring or synthetic drugs [78]. Uniformity is important when synergists are involved as relatively small variations in the ratios can have large effects on the overall phytochemical activity.

Plant genetics has opened exciting possibilities for cultivars and pharmaceutical development. The ability of the fresh plant material to efficiently produce THC and CBD is governed by inheritance of either of two codominant genes, B_T and B_D [79]. A proportion of plants in a natural population inherit a B_T gene from each parent and those homozygous for the gene will produce the enzyme THC synthase enabling the biosynthesis of THC in satisfactory quantities, while producing CBD at near undetectable levels. Others inheriting and thus homozygous for the B_D genotype will produce CBD and minimal THC. The third heterozygous B_TB_D category that results from inheritance of each gene with produce both enzymes resulting in biosynthesis of a more even mixture of THC and CBD. In natural settings however, large variations in ratios between these two cannabinoids are found in the heterozygous siblings of any parental cross. Modern plant breeding techniques have made it possible to breed new parental crosses where both parents are female. Male cannabis plants now play little or no part at GW Pharmaceuticals in cannabinoid production or breeding.

Induction and maintenance of flowering are important aspect of medical cannabis production. The cannabinoids and other terpenes are found in varying ratios in all aerial parts of the plant, but female flowers are the main source of most cannabinoids. Together they cluster in large numbers on a branch or a system of branches termed an inflorescence. The latter are

categorized on the basis of the arrangement of flowers on a main axis (peduncle) and the timing of its flowering (as determinate and indeterminate). Keeping the plants seedless by preventing pollination induces new flowers to develop and the formation of unnaturally large inflorescences. Within these unpollinated inflorescences cannabinoid biosynthesis is advantageously prolonged and the produced marijuana is exceptionally potent termed insemilla. The cannabinoids are secondary metabolites only indirectly involved in the normal growth, development, and reproduction of an organism, and as it is widely accepted, they are predominantly, if not entirely, synthesized and sequestered in microscopic structures called capitate or glandular trichomes. Most of the essential oils such as the monoterpenes and sesquiterpenes, found in cannabis, are also located in these structures. GW Pharmaceuticals routinely seeks genotypes with the maximum yield or purity of a secondary metabolite [76].

Achieving a mature cannabinoid profile at harvest requires an understanding of the rapid changes in the profile of cannabinoids over the course of the plants growth. In the early and late phases of growth, the enzymes synthesizing THC or CBD have a very similar turn-over rate (kcat), and affinity (Km) for their substrate. Variation in THC and CBD ratio in Sativex® is assured by including homozygous chemotypes in the formulation and routinely harvesting them at fixed periods of growth such as when CBG (the precursor of THC, CBD and CBC synthesis) increases intermediate between the early and late phases of plant growth.

Growing and harvesting conditions are also important determinants of uniform, cannabinoid-rich cannabis including the provision of stable bright lighting. Glasshouses raise irradiance levels whenever natural lighting conditions are below a tolerable minimum, and during the winter lamps can provide the necessary light energy. Photosynthesis and resultant growth is markedly affected by temperature with an optimal range from 25°C to 35°C for cannabis plants worldwide. Plants are typically grown in pots and hand-watered until roots are established, and thereafter watering is automated. Pesticides are generally avoided and averted by rigorous cleaning regimes. To minimize bacterial and fungal spoilage, crops are cut at the base and promptly dried in warm, dehumidified and ventilated conditions. The

conversion of the cannabinoid acids into neutral cannabinoids, which requires the removal of carboxyl groups is achieved by uniformly heating the dried material under controlled conditions and precise timing. To produce a cannabis extract, batches of dried plant material are immersed in liquid carbon dioxide at extremely high pressure. The ingredients dissolving in this solvent are then separated and purified.

PROCESSING AND
EXTRACTION TECHNIQUES

Plants are natural resources presenting an important economic potential in health and wellness. This added value is directly related to the extract composition. This composition determines its physicochemical properties. Hence, the medicinal gain of an effective extract relies upon the extraction methods of the secondary metabolites [80] and the analysis and identification of them [81]. State of the art technology is vital for the extraction of active phytopharmaceutical ingredients from marijuana. Extraction operations can be optimized and highly controlled to produce pharmaceutical-grade cannabis products. The two primary active agents extracted for medicinal use are THC and CBD, but may include any of the other 70 cannabinoids in the *Cannabinaceae* family. The goal of the extraction process is to produce precise compositions of the active products, each with ingredients that will yield the desired therapeutic effects at pharmaceutical dosages.

In recent time, there has been an emphasis on the recovery of high value-added products by using sustainable technologies. One of the ways to achieve this is the application of supercritical fluids. Applied as solvents for precipitation, as reaction media, and as the mobile phase for chromatography and solvent extraction, supercritical fluid extraction (SFE) [82-84] is the

most investigated process. From an economic point of view, technologies involving elevated pressures require high investment costs for high–pressure equipment. Because of this, it is reasonable to apply SFE for the separation of components with high added value, such as nutraceuticals, pharmaceuticals, food additives, and other components with high feed-to-solvent (F/S) extraction ratio. SFE is a separation process where solid or liquid matter is processed in order to obtain soluble compounds from mixtures. Supercritical fluid extraction offers a variety of applications due to specific properties, which can be relatively easily adjusted with changing pressure and temperature. A fluid above critical temperature has gas-like viscosity, liquid-like density, and its diffusion magnitude is of order between the two fluid states. The mass transfer of the solute in the supercritical solvent will depend upon the solubility of the solute in the given solvent. Different compounds have different solubilities at various operating conditions. In general, temperature and pressure have the biggest influence on the solubility of compounds in supercritical fluids. Temperature has two competing effects on solubility. First, increasing the temperature at constant pressure decreases the density of the solvent. Thus, solubility of the solute is decreased. On the other hand, by increasing the temperature at constant density, the vapor pressure of the solute is increased. Therefore a solute is more soluble in a supercritical fluid. Which effect will prevail depends on the properties of the system. The effect of pressure is more direct. With increasing the pressure of a supercritical medium, higher densities are achieved. The higher the density of the medium, the higher the solubility of the solute. The most common solvent used as a supercritical fluid is carbon dioxide (CO_2).

Modern methods of extraction employ supercritical fluid extraction (SFE) using CO_2 have been utilized in the food, beverage, fragrance and phytopharmaceutical industries for decades. Another prominent example of the application of SFE combined with CO_2 as the solvent, is in the decaffeination of coffee from its solid natural substrate, the coffee bean. The process of CO_2-based SFE as the solvent has gained traction among herbal supplement producers for the elimination of undesired pesticides and metals from plants without adulteration of the beneficial elements. This process has

been translated into extraction of active pharmaceutical agents from the cannabis plant.

By passing over a substance such as pulverized marijuana, and suffusing the plant material with supercritical CO_2, SFE dissolves desired substances away from the solid plant mater as if it was a liquid. The process requires talented operators using precision equipment to extract various cannabinoids and terpenes from the plant material, separately from one another. This has obvious therapeutic benefits, as different cannabinoids are useful in different health conditions. In fact, an entire array of cannabinoids can be extracted all at once, preserving what is known as the entourage effect. SFE has been applied previously to cannabis by several authors, but mainly to extract oil from Hemp seeds (*Cannabis sativa L.*). Results on seed oil composition obtained at different process conditions [85, 86], oil oxidation stability [87], oil antioxidant capacity [88], recovery of volatile compounds [89], and extraction and solubility parameters determination [90] have been reported. Naz and colleagues [91] compared SFE with traditional distillation methods of hydrodistillation (HD) and steam distillation (SD) in the isolation of aromatic compounds from Cannabis indica and Cannabis sativa SFE with noting high yields of essential oil using SFE. Rovetto and Aieta [92] described supercritical carbon dioxide extraction of cannabinoids from *Cannabis sativa L.* noting that when ethanol was applied to modify solvent polarity and enhance the extraction process, the extraction rate was improved and a lower solvent to feed ratio was required to achieve high yields. The authors proposed a new extraction strategy in the supply of co-solvent in the form of pulses noting that a pulse regime showed a better performance than the traditional co-solvent at constant concentration in the solvent flow, with major impact on plant material with low cannabinoid concentration. The pulse regime reached the same extraction efficiency with lower solvent and much lower co-solvent consumption at a shorter extraction time.

One industry leader utilizes an eight step extraction approach. After the cannabis has been grown, harvested and cured, it is sent to a laboratory for analysis. This will inform the extraction personnel how best to approach the extract. If the plant is high-CBD, the extraction staff may prefer to target that

fraction rather than another compound that is not as prevalent. In that regard, the extraction process is informed by the plant chemotype. Next, the plant material is mechanically ground into fine particles to maximize the surface area presented to the CO_2 solvent. Generally, the substrate consists of flowers, flower-proximal leaf and flower-proximal stems and petioles. The larger, flower-distal meristem and fan leaves are generally discarded. The pulverized, cannabinoid-rich plant material is transferred to a pressure vessel to a predetermined volume into which CO_2 is pumped. The resistance of the exit valve determines pressure, which determines temperature and in turn, the solvency power of the CO_2. In this manner cannabinoid fractions can be targeted for extraction. Supercritical CO_2 exits the pressure valve with the targeted cannabinoids in solution. At this stage the pressure is released and the CO_2 (solvent) escapes as a gas where it is recaptured. This leaves behind the extracted cannabinoids (solute). CO_2 exiting the pressure vessel is recaptured and recycled through the pulverized material. The process of dissolution, depressurization and deposit of cannabinoids repeats until complete. The flow rate, pressure and ratio of solvent to solute all determine which cannabinoids are extracted. When a pressurized fluid is quickly depressurized it flashes into vapor, leaving behind the solute it was carrying. In this manner, the cannabinoids can be separated by flashing the CO_2 into various levels of depressurization (using a series of variously-pressurized drums). Lastly, the pressure vessel is emptied, and the starting material has been stripped of its useful cannabinoids with the cellulosic fibers remaining that can be discarded as waste. Extract from the supercritical CO_2 process can be washed in ethanol (EtOH) to remove plant waxes and lipids, preserving the cannabinoids and terpenes, and this product can be further refined using vacuum distillation. The extracts can be boiled using vacuum evaporators at various temperatures, which removes the more volatile compounds first, enabling a more accurate level of refinement. No solvent is used in this process. As a final and most-accurate level of refinement, supercritical CO_2 chromatography can be used to achieve a 99% level of purity for the various cannabinoids and terpenes.

The collected fractional plant extract may undergo further refinement using filtration, distillation and chromatography techniques. Initial phase

removal of undesired components is achieved by precipitation in a low molecular weight alcohol, specifically 100% food-grade ethyl alcohol, followed by sequential plate filtration steps, and eventual evaporation of the undesired alcohol. Evaporation of the alcohol is performed within a completely contained vacuum-assisted evaporator, which is conducted within a properly vented enclosure that meets and exceeds all relevant OSHA and ANSI Z9.5 standards and guidelines. The resulting cannabis extracts are further refined using thin-film evaporation plates and vacuum-assisted heating. Recovery of the target therapeutics occurs post decarboxylation of the carboxylic acid on the aromatic moiety of the cannabinoids, which is performed under vacuum by heating the compounds to 120-130°C for varying periods of time. Typically, this process is conducted using thermally controlled vacuum ovens and chemical-resistant vacuum pumps, ensuring all vapors are captured using in-line traps. The entire process is conducted in a properly ventilated lab space.

Further refinement of the cannabinoid rich oils may be desired where terpenes and other light essential oils are undesired. Vacuum-assisted molecular distillation techniques (short-path, spinning-band, wiped-film) are employed to isolate cannabinoid fractions where high purity cannabinoid oils are desired. Cannabis extract can be charged into a low-pressure environment and heated incrementally to "boil off" components. Ideally this is performed while minimizing heat treatment and minimizing cross-contamination between fractions. No solvents are utilized nor any flammables produced during the process. The vacuum assisted distillation enables lower temperatures to be used and prevents thermal degradation or denaturing of the therapeutic compounds. The captured cannabinoid-rich fraction can be used directly in pharmaceutical dosage forms. In the cases where pure isolates of the cannabinoids are desired, supercritical fluid chromatography (SFC) is utilized. Due to the intrinsic similarities in structure and boiling points of many of the cannabinoids and cannabis essential oils, chromatography is utilized to achieve high purity (98%+) separations of individual compounds. SFC can be performed using CO_2 and ethyl alcohol with high throughput and high resolution, thus making it more advantageous than typical HPLC and GC methods. Custom formulations for

targeting ailments can be accomplished by utilizing these high-purity isolates of individual cannabinoids in conjunction with specific high-purity terpenes.

PRODUCTS

Several medical cannabis products available for human consumption by law include (1) pills, (2) oils, (3) topical forms such as gels, creams and ointments, (4) products appropriate for administration by vaporization or nebulization, (5) tinctures, (6) and liquids. Solvent-based extractions produce concentrates in varying degrees of viscosity ranging from nearly solid to free-flowing. These properties, in turn, determine the range of potential formats for each type of extract. In other words, it is not possible to make a sublingual spray out of a waxy extract. It would first have to be thinned into a solvent suitable for human consumption. For the solid products, each unit will have a maximum discreet dose of 10mg active substance per unit. For liquid products, the dose will be limited to 10mg of active ingredient per gram of product. Oral capsule/tablet, tincture/syrup/solution for gastrointestinal oral consumption; sublingual lozenges and sprays; epicutaneous topical balms and ointments; and inhaled vaporized products are commonly marketed. By providing multiple form factors and dosages, patients can apply the medicine to promote local or systemic effects, vary the rate of drug delivery into the body, and consumed at distinct doses, or self-regulate the amount consumed. All such products entail a rigorous process of standard operating procedures to ensure product safety, consistency, and efficacy.

Gelatin or vegetarian based capsules provide quick dissolution and delivery of the active pharmaceutical agent via the gastrointestinal path. Capsules are easy to manufacture, provide discrete controlled doses, and are readily absorbed into the body. They are odorless, easy to swallow and less susceptible to oxidative degradation than tablets. A capsule will be loaded with varying amounts of custom compositions of the agent (e.g., 5 mg CBD, 5 mg THC, 1 mg CBN) depending upon the medicinal use. Tablets provide

very discrete dosages and are incorporated with controlled release agents, providing time-release drug delivery.

Sublingual products dissolve or disintegrate in the mouth to deliver the active pharmaceutical agent. The advantage of a sublingual lozenge is its discrete dosage in each unit. A lozenge may be loaded with varying amounts of custom compositions of APIs (e.g., 5 mg CBD, 5 mg THC, 1 mg CBN) to target different medical needs.

Liquid. Tinctures and solutions of dosage-ready oils are diluted in an alcoholic/hydroalcoholic solution to form a tincture of specified concentration (e.g., 5% wt. API). This tincture is self-administered in droplet portions via oral ingestion. The tincture rapidly absorbs into the body via submucosal route of administration.

Medical marijuana can be concentrated into vaporizer cartridges designed for inhalation. These cartridges are designed with a ceramic core surrounding a radial heating element that is activated by an external power supply (battery). Inhalation on the cartridge while heating reduces the pressure and therefore vaporizes the oil and target compounds. This process transfers the therapeutic agents into the lungs for rapid delivery of the APIs into the blood stream. Vaporizing rather than combusting prevents degradation of the active pharmaceutical agent and potential generation of undesired combustion products, some of which may have potentially detrimental constituents.

PATIENT SATISFACTION

The Netherlands has been intensively studying patient and production satisfaction for decades, even before it was legalized for medical use in 2003. Founded in 1995, Maripharm, a nonprofit patient-oriented organization, delivers medical-grade cannabis (MGC) on prescription to pharmacies throughout the country. When a patient presents a prescription for MGC, the pharmacy forwards the prescription to Maripharm, which delivers units of 25 or 5 g of standardized, sterile, and vacuum-packed MGC to the pharmacy. The THC content in MGC is standardized at 10.2%.

Gorter and colleagues [93] developed a standardized questionnaire about the medical use of cannabis in the Netherlands to obtain information from patients and physicians prescribing MGC. The questionnaire documented the indications for which MGC was taken, the duration, whether the patient had any side effects, and whether the patient was content with the effects of cannabis. Each shipment of MGC was accompanied by two questionnaires, completed by both patient and prescribing physician. This provided documentation of the indications for which MGC was taken, the duration, whether there were medication side-effects, and if the patient was content with the effects of cannabis. Among 107 participants of mean age 58 years, the main reported diagnoses for which MGC was prescribed were neurologic disorders like MS and spinal cord injuries (n = 45; 38.8%), musculoskeletal/connective tissue disorders (n = 24; 20.7%), and malignant tumors for symptoms like anorexia/cachexia and fatigue (n = 16; 13.8%) and "other" which were often HIV infection, cerebrovascular accident, and pain (n = 31; 26.7%). Of the 107 questionnaires evaluated in this study, 66 patients (64.1%) documented a good or excellent effect for their symptoms. Of these patients, 44% used cannabis for > = 5 months. It is likely that benefiting patients continued taking cannabis for the relief of their symptoms, while others, not experiencing a benefit during the first few weeks to months, might have stopped within 1 to 4 months. In addition, lack of efficacy experienced in the first few months might be attributed to certain medicinal effects of cannabis that take a while to take effect, such as appetite stimulation, weight gain, and mood elevation. The evaluations of efficacy and side effects by physician and patient were similar. Therefore, it is likely that both patients and physicians were equally content or disappointed with regard to the medicinal effects of the cannabis.

Tibor and colleagues [94] assessed the therapeutic satisfaction within a group of Netherland patients using prescribed MGC and compared the subjective effects among the available strains with special focus on the TJC and CBD content. In a cross-sectional and natural design, users of MGC were investigated with questionnaires. Medical background of the patients was ascertained as well as experienced therapeutic effects and characteristics of cannabis use. Subjective effects were measured with psychometric scales

and used to compare among the strains of cannabis used across this group of patients. Among 102 patients so studied of mean age 53 years, chronic pain (53%; n = 54) was the most common medical indication for using cannabis followed by multiple sclerosis (23%; n = 23), and 86% (n = 88) of patients (almost) always experienced therapeutic satisfaction when using pharmaceutical cannabis. The differences found among the available strains in this study confirmed the hypothesis that THC/CBD content is important to the ultimate effect experienced. CBD is a cannabinoid with quite distinct effects from THC, and the lack of psychotropic, unwanted, effects of CBD has generated widespread scientific interest into its therapeutic potential against inflammatory diseases and cancer. In addition, CBD has gained a lot of interest because of its antipsychotic properties and capacity to counteract THC's adverse effects. The current results suggest that CBD may have a modulatory effect on some of the THC's well-known subjective adverse effects, such as anxiety or depressed mood. Therefore, it is very interesting to see that the strain with high-CBD content was associated with less anxiety and feelings of dejection. The pharmacologic composition of the different strains available affected the extent of different subjective (adverse) effects, with a high-THC/low-CBD product leading to more appetite stimulation but also to feelings of dejection and anxiety in comparison with a low-THC/high-CBD product.

Chapter 7

INDICATIONS FOR MEDICAL CANNABIS

NEUROLOGICAL DISORDERS

A wealth of data from clinical trials employing specific and non-specific synthetic endocannabinoid receptor agonists as well as, plant-based cannabinoids show promising approaches to the management of diverse neurological and cancer-related disorders, typically refractory to conventional management. Koppel and colleagues [15] conducted the first systematic review of randomized clinical trials (RCT) of CBM in the treatment of diverse neurological disorders from 1948-2013. In that analysis the authors render an assessment of the cited studies, categorizing them by Class I-IV, from most to least robust RCT, according to the classification system of the American Academy of Neurology (AAN) [95] for therapeutic interventions.

ADULT AND CHILDHOOD EPILEPSY

Epilepsy is a common brain disorder accounting for approximately 1% of the global burden of disease with an incidence of 33 to 57 per 100,000 person-years [96], with a lifetime risk of 1.3% to 4%. In epilepsy, drug

resistance is defined as failure to stop all seizures in a patient who has had adequate trials of at least two appropriate medications [97]. Of those afflicted with epilepsy, about one-third are drug-resistant [98]. In these patients, the ability of current medications to stop all seizures is often dismal. Thus there has been intense interest in the development of new medications with anti-epileptic properties, particularly those that affect novel receptors, in the hope of helping the patients in whom current agents are ineffective.

Previous studies have documented deficiencies in endocannabinoids in temporal lobe epilepsy (TLE) patients as well as a rise in anandamide concentrations post-seizures in mice, suggesting an anti-seizure activity profile [16]. The most extensively studied exogenous cannabinoid compound, THC, is a partial agonist at both CB_1 and CB_2 receptors and achieves its psychoactive properties likely through modulation of gamma-aminobutyric acid (GABA) and glutamine. The other exogenous cannabinoid compound, cannabidiol (CBD), does not appear to bind to either CB_1 or CB_2 but does possess neuroprotective and anti-inflammatory effects. Its inhibition of cyclooxygenase and lipoxygenase which leads to inverse agonism at CB_1/CB_2 receptors, renders it effective in epilepsy through modulation of the endocannabinoid system. CBD retards the degradation of the endocannabinoid N-arachidonoylethanolamine (anandamide), which binds CB_1 and CB_2, and may have a role in inhibiting seizures. Marijuana has been used since the 19th century for patients with epilepsy. One patient from that time was described whose seizures stopped when marijuana was given and returned when marijuana use was stopped [99]. There have been other anecdotal reports of its efficacy in humans.

There are several theories of the origin of epilepsy and the effect of cannabinoids on the brain. The most common kind of epilepsy in adults arises from changes in the hippocampus which is involved in the transformation of short term memory into long term memory. One of the changes which occurs involves a neuronal subpopulation of the hippocampus called the granule cells. These cells undergo aberrant synaptic reorganization known as mossy fiber spouting. Such histologic changes occur in the human epileptic hippocampus even without hippocampal sclerosis [100]. This fiber sprouting synapses with another type of cell called

granule cells. However, animal models have shown that this then forms an excitatory feedback loop [101] which can be the underlying mechanism for seizures. In an animal model of seizures, endogenous release of cannabinoids with an excitotoxic agent led to worse and more deadly seizures in mutant mice without CB_1 receptors than in wild-type mice [102], suggesting a protective effect of cannabinoids. In human hippocampus resected for epilepsy surgery, recordings of granule cells show a reduction of inhibition with a CB_1 agonist [103]. This is likely due to depolarization-induced inhibition of gamma-aminobutyric acid secreting (GABAergic) cells. One explanation is that cannabinoids decrease inhibition of aberrant inhibitory cells. The existence of such aberrant inhibition is seen in epileptic rats [104]. Another possible mechanism for the protective effect of cannabinoids involves N-methyl-D-aspartic acid (NMDA) receptors. NMDA receptors are glutamate receptors, which play a crucial role in learning and memory. One synthetic cannabinoid appears to block NMDA receptors in a rodent model at a different site to other non-competitive NMDA antagonists [105].

A Cochrane Review [106] assessed the efficacy and safety of cannabinoids used as monotherapy or add-on treatments in adult individuals with epilepsy identifying in blinded or unblended RCT. The primary outcome was seizure-free status at one year or more, or three times the longest interseizure interval. Secondary outcomes included responder rate at six months or more, objective quality of life data, and adverse events. The authors found four randomized trials that included a total of 48 patients, each of which used cannabidiol as the treatment agent. Anti-epileptic drugs were continued in all studies. Details of randomization were not included in any study report. There was no investigation of whether the control and treatment participant groups were the same or different. None of the patients in the treatment groups suffered adverse effects. A dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients generally for short periods of time but generally not long term. Cunha and colleagues [107] studied 15 patients with TLE with secondarily generalized seizures, with at least one generalized seizure weekly. These patients received 200 to 300 mg of cannabidiol daily or placebo. The patients

received the medication for as long as 4.5 months and seizure frequency was reported. The patients tolerated cannabidiol without toxicity. Ames and coworkers [108] studied 12 patients institutionalized due to mental retardation with uncontrolled seizures were given three capsules of sunflower oil (as placebo) or sunflower oil and 100 mg of cannabidiol for the first week (as treatment). Patients received 300 mg of cannabinol daily for the first week. During the next three weeks (weeks two to four) the patients were given two capsules, so for those in the treatment arm they received 200 mg of cannabidiol daily. There were no differences in seizure frequency between the two groups, although no details were given. The only side effect was mild drowsiness. Mechoulam and colleagues [109] studied 9 patients who were randomized to either 200 mg of cannabidiol or placebo. Patients were treated with their habitual medication and either cannabidiol or placebo for three months. Two of four patients treated with cannabidiol achieved seizure freedom for the three months of treatment, and none of the five treated with placebo were described as experiencing improvement. No toxic effects were observed. Trembly and coworkers [110] published an abstract from a conference citing 12 patients treated with a single-blind placebo for six months followed by double-blind 300 mg of cannabidiol or placebo in a cross-over trial lasting an additional 12 months. Ten patients in the trial did not have changes in the seizure character or frequency, and did not suffer any side effects.

Campbell and colleagues [111] reviewed cannabinoids in pediatric epilepsy. According to Cilio and colleagues [112], in the case of pediatric epilepsy, parents are making the decision to use cannabidiols because of prominent international and national median attention, reports of children successfully treated, and the belief that treatments derived from natural products are safer and more effective than medication. The most famous case, documented on cable television was that of Charlotte, who suffered from status epilepticus, who having failed medication, developed significant cognitive delay and sought help from a dispensary in Colorado who manufactured an oral, liquid, high-concentration CBD-to-THC strain of cannabis [113]. Dubbed Charlotte's Web, in three months she was 90%

seizure-free and by 20 months, she was cognitively improved suggesting reversible epileptic encephalopathy.

In a retrospective chart review of parental reporting the response to oral cannabis extracts for treatment of refractory epilepsy in 75 children and adolescents younger than 18 years, Press and colleagues [114] cited improvement in 57% of children in seizure frequency, with a third reporting > 50% reduction in seizure frequency, with concomitant improvement in behavior, alertness in 33%, and language and motor skills each in 11%. Major adverse side effects were somnolence and gastrointestinal symptoms in < 12%. In a Facebook survey administered to 150 parents of children with treatment-resistant epilepsy, investigators at Stanford University [115] noted that 84% of 19 affected children experienced an 84% reduction in seizure frequency, 12 of whom were able to be weaned off of another epileptic medication. There was in addition, improved mood, alertness, and sleep. In fact, with most orphan drug designations employing CBD for pediatric seizures, a search of ClinicalTrials.gov identified 2 active studies, one observational cohort time perspective study of CBD [116].

DEMENTIA

Dementia is a growing epidemic across the globe. Alzheimer disease (AD) is the commonest dementing illness in the elderly. Although the risks associated with AD are multifactorial, the greatest risk factor by far is aging [117]. The age-specific risk of AD dramatically increases as individuals get older; findings from the Framingham study in the early 1990s showed that the incidence doubles every five years up to the ages of 89 years [118]. With global reductions in fertility and extended life expectancies, the number of patients with AD is expected to increase as populations age [119]. In the United States, it is estimated that approximately 5.3 million people had AD in 2015; 5.1 million people being 65 years and older and approximately 200,000 people under the age of 65 years with early onset AD (EOAD) [120]. It is estimated that the number of new cases of AD and other

dementias will at least double by 2050 and substantially increase the socioeconomic burden worldwide [121].

Cholinesterase inhibitor drugs, such as Donepezil, are currently used to treat AD and can improve cognitive symptoms, activities of daily living and behavior. However, treatment effects are small and they only act to delay an inevitable decline by around 9 to 12 months [122]. At least half of patients with dementia will experience behavioral and psychological symptoms (BPSD) such as agitation, aggression and psychosis leading to significant caregiver stress [123]. Such symptoms are distressing for the patient, and may prompt placement in a residential facility or nursing home. Antipsychotic drugs are widely used to treat BPSD but have only modest efficacy [124]. Use of these drugs in dementia is also associated with serious side effects including an increased risk of cerebrovascular adverse events and death. It has been shown recently that the cholinesterase inhibitor Donepezil has little benefit in the management of BPSD [125]. Accordingly there is a need for new, safe and more effective treatments for dementia and its associated symptoms. The cannabinoids are one potential agent under investigation for the treatment of dementia.

Krishnan and colleagues recently reviewed cannabinoids for the treatment of dementia [126]. Several neurobiological effects of cannabinoids have been demonstrated which could be relevant in the treatment of dementia. The main function of the endogenous cannabinoid system is thought to be the regulation of synaptic transmission and this process can be disordered in many neurological conditions including dementia. Studies are also beginning to provide evidence of the neuroprotective effects of cannabinoids. CB_1 receptors have been shown to regulate processes such as excessive glutamate production and subsequent oxidative stress, which can damage neurons and lead to neurodegeneration [127]. *In vitro* experiments have demonstrated that cannabinoids can protect neurons from this type of excitotoxic damage and from hypoxic damage. There is also some evidence that CB_2 receptors may be involved in neuroprotection by reducing neuroinflammation [128]. Neurodegeneration is a feature common to the various types of dementia and the neuroprotective

effects of cannabinoids may therefore be beneficial in slowing the progression of these diseases.

Cannabinoids may have more specific effects in AD pathology. THC diminishes acetylcholinesterase-induced amyloid beta-peptide aggregation, the key pathological marker of Alzheimer's disease [129]. THC competitively inhibits the enzyme acetylcholinesterase (AChE)-an effect similar in action to the anti-dementia drugs like Donepezil. Intracerebroventricular administration of a synthetic cannabinoid (WIN55, 212-2) in experimental rats with an amyloid beta-peptide model of AD leads to a prevention of their cognitive deficit and decreased neurotoxicity [130]. These studies suggest that cannabinoids could interrupt the disease process as well as treat symptoms in AD.

There have been several clinical studies examining the effects of cannabinoids on symptom management in dementia. A small open-label pilot study showed that daily administration of dronabinol (synthetic THC) reduced night-time motor activity and agitation in patients with dementia [131]. Volicer and colleagues [132] showed that dronabinol improved weight gain in a small group of patients with AD who were refusing food when compared with placebo. Preliminary data also suggest that cannabidiol may be an effective hypnotic [133]. Volicer and colleagues [132] performed a placebo-controlled crossover trial investigating the effects of dronabinol in 15 patients with a diagnosis of probable AD and BPSD. Dronabinol treatment decreased severity of disturbed behavior and this effect persisted during the placebo period in patients who received dronabinol first. Walther and colleagues [131] reported the results of an open-label pilot study of six consecutive patients in the late stages of dementia, suffering from BPSD. Five patients with Alzheimer's disease and one patient with vascular dementia-were treated with 2.5 mg dronabinol daily for 2 weeks. Motor activity was measured objectively using actigraphy. Dronabinol led to a reduction in nocturnal motor activity ($P = 0.028$). These findings were corroborated by improvements in Neuropsychiatric Inventory total score ($P = 0.027$) as well as in subscores for agitation, aberrant motor, and nighttime behaviors ($P < 0.05$). Liu and colleagues [134] summarized the recent literature investigating cannabinoids for agitation and aggression in AD.

Citing significant benefits from synthetic cannabinoids, dronabinol or nabilone, on agitation and aggression noting however that most studies were small in sample sizes with short trial duration, and lack of placebo control in many. Van den Elsen [135] conducted the largest RCT so far studying oral THC in neuropsychiatric symptoms (NPS) in dementia, with valid and rigorous trial methods noting that a 4.5 mg oral low-dose of THC was not only extremely well-tolerated but reduced NPS symptoms similar to controls at day 21 which allows for future studies of higher doses.

There is a growing need for effective and safe interventions for individuals with dementia. For the present, THC is a safe and well-tolerated mode of treatment for the NPS symptoms of dementia. Further systematic reviews in this area will help inform healthcare workers, researchers, and other public health decision makers.

MULTIPLE SCLEROSIS

Evans and colleagues [136] reviewed the incidence and prevalence of multiple MS in the Americas noting high heterogeneity among all studies. An epidemiological study from the Mayo Clinic estimated MS prevalence and incidence in the United States (US) from 1985 to 2000 in Olmstead Country Minnesota [137] noting age-standardized rates (ASR) of 191.2 per 100,000 and 7.3 per 100,000.

A meta-analysis evaluating prevalence estimates from 59 countries found a statistically significant latitudinal gradient for prevalence even after age-standardization and adjustment for prevalence year [138]. Prevalence estimates of MS were much lower in South America compared to North America. Geography alone may not predict the prevalence or risk of MS.

MS is classically divided into relapsing-remitting (RRMS) pattern noted in about 85% of cases, and a chronic progressive pattern known as primary progressive MS (PPMS) in about 10% of case. One-half of those with RRMS may evolve into secondary progressive MS. Discrete episodes of neurological dysfunction develop over hours to days and are called relapses, flares, attacks, or exacerbations. Attacks may be quite devastating, though

most patients recover well. Occasionally, however, attacks can be debilitating if left untreated, especially if the brainstem or spinal cord is involved. During a severe exacerbation, inflammatory damage to myelin affects underlying axons which can lead to poor recovery and permanent disability. Unlike RRMS, PPMS presents equally in men and women, and tends to occur at an older age. Certain presentations, such as optic neuritis, that are common in RRMS, are rare in PPMS compared with RRMS. The diagnosis of MS is based upon two discrete episodes of neurological dysfunction at least 30 days apart in different locations of the CNS, alternatively, in those with one relapse who show evidence of dissemination in time and space (abbreviated DIT and DIS) on magnetic resonance imaging (MRI), while excluding alternative diagnoses through clinical, radiographic, and laboratory methods.

Treatment can favorably impact MS by immune modulation, enhancement of myelination, improvement of conduction through demyelinated pathways and providing symptomatic improvement without directly affecting the underlying pathology. Immune modulatory therapy diminishes the activation and proliferation of immune cells and their migration into the CNS by enhancing intrinsic suppressor activity or limiting the destruction caused by inflammatory processes. Acute exacerbations are initially treated with corticosteroids, which enhance the resolution of symptoms and signs, though do not significantly affect the long-term outcome of an exacerbation. Pulse therapy with corticosteroids is associated with many temporary side effects such as insomnia, irritability, fluid retention, increased appetite, weight gain, hyperglycemia, hypertension, dyspepsia, depression, psychosis, bone fractures, and osteoporosis. Plasmapheresis and intravenous immune globulin (IVIg) are used in severe relapses, refractory to corticosteroids. Biological therapies focused on improving CNS conduction amplify and prolong action potentials, however they may be associated with seizures and encephalopathy.

Symptomatic therapy is one of the most important aspects of treatment for symptoms not fully controlled with management of the primary disease processes [139]. Spasticity is the most disabling and common symptom of MS, reported in up to 84% of patients, with an increasing presence and

severity as the disease progresses. MS-related spasticity (MSS) substantially impairs activities of daily living (ADL) including day-to-day hygiene, dressing, mobility, eating and housework, as well as occupational and social activities. Although spasticity is very common in MS, there are a limited number of available treatment options including intensive physiotherapy, oral drugs (notably baclofen and tizanidine), focal intramuscular injections of botulinum toxin A and intrathecal baclofen.

An overactive bladder (OAB) leading to nocturia, urgency, urinary frequency, and incontinence that disrupts patients' daily routine and reduce quality of life (QoL) occurs in the majority of patients with MS. Currently available treatments include diet modifications, bladder training or planned voiding, limiting fluid intake which may lead to dehydration and other potentially dangerous complications, medications in a variety of forms, pelvic floor physical therapy to target overactive muscle groups attached to the pelvic bone and sacrum, biofeedback, neuromuscular stimulation, percutaneous nerve stimulation, intermittent self-catheterization, and surgical intervention.

Central pain occurs in up to one-half of patients with MS, and as many as a third of affected patients regard pain among their most severe symptoms, characterizing it as frequent, disabling, and inadequately managed. The most common form of central pain in MS is nonparoxysmal extremity pain which shows large interindividual variation and may manifest with several, typically dysesthetic qualities such as burning, aching, pricking, stabbing or squeezing. Painful extremity spasms are characterized as central pain.

Interest in the use of CBM followed early observations of the success of relieving symptoms of experimental encephalomyelitis with cannabinoid receptor agonists [140] and other preliminary studies demonstrating modest positive effects of a synthetic cannabinoid analogue on neuropathic pain of mixed etiology, and of whole plant-derived CBM on neurogenic symptoms including pain in MS patients [141; 142].

A multicenter RCT by Zajicek and colleagues [143], rated Class I, of oral cannabis extract (OCE) containing THC and CBD, titrated to maximum daily dose of 25 mg THC was effective in reducing patient-reported scores

over the study period of 15 weeks in 277 patients with stable MS stratified by walking ability and use of antispastic medication. A second multicenter RCT by Zajicek and coworkers [144], rated Class I, of 630 patients with MS-related spasticity who received THC or a combination of THC and CBD for 8 weeks demonstrated beneficial effect for both active treatments on secondary outcomes of patient-reported spasticity and central pain. A third multicenter RCT by Wade and colleagues [145], rated Class I, of 160 patients that compared self-titrated nabiximols with placebo for treating the most troublesome symptom measured by a 100-point visual analog scale (vAS) showed a significant reduction in VAS rating compared to placebo. A fourth RCT, a 12-month continuation study by Zajicek and coworkers [146], rated Class II, because of loss at follow-up reported improved Asthworth scores [147] from study beginning to end in patients treated with THC or THC/CBD extract adjusted for ambulatory status demonstrated improvement in Ashworth score from study beginning to study end.

More recently, Flachenecker and colleagues [148] conducted the Mobility Improvement (MOVE) 2 Study with the aim of evaluating the clinical outcomes and safety of nabiximols in clinical practice assessing outcome tolerability, QoL and treatment satisfaction in MSS patients initiated on nabiximols. After 1 month, nabiximols provided relief of resistant MSS in 74.6% of patients with mean spasticity 0-10 numerical rating scale (NRS) scores that decreased from 6.1 ± 1.8 to 5.2 ± 2.0 points, $\geq 20\%$ of mean NRS score decreased by 40%. After 3 months, 55.3% of patients had continued to use nabiximols and the mean NRS score decreased by 25% from baseline. The authors concluded nabiximols were an effective and well-tolerated clinical practice treatment option for resistant MSS. A follow-up 12-month prolongation of the MOVE 2 study [149] in 52 patients showed a significant decrease in the mean spasticity NRS from 6.0 ± 1.8 points at MOVE 2 baseline to 4.8 ± 1.9 points after 1 month (4.5 ± 2.0 points); and a further decrease after 12 months to 4.3 ± 1.9 points). The majority of patients (84%) did not report adverse events. The authors

 concluded that nabiximols showed long-term efficacy and tolerability in the treatment of resistant MSS in everyday clinical practice.

As regards to the treatment of MS-related central pain with CBM, Rog and colleagues [150] carried out a RCT rated Class I , in 66 patients with MS-related pain and spasticity, randomized to nabiximols or placebo, and rated their pain on an 11-point NRS noting the superiority of active treatment in reducing pain intensity. THC or nabiximols were probably effective for treating MS-related pain and painful spasms in a previously described Class I RCT conducted by Zajicek and colleagues [144] noting pain reduction after 14 weeks of treatment with THC and THC/CBD compared to placebo.

In regards to bladder dysfunction in MS, efficacy of nabiximols was noted in an RCT conducted by Kavia and coworkers [151], rated Class I, of 135 patients with MS and detrusor overactivity treated with nabiximols in reducing the number of bladder voids per day at 10 weeks. Improvement in incontinence QoL was in favor of Sativex® over placebo but did not reach statistical significance.

NEUROPATHIC PAIN

Neuropathic pain is regarded as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Central neuropathic pain originates from damage to the brain or spinal cord, while peripheral neuropathic pain stems from damage to the peripheral nerve, plexus, dorsal root ganglion, or roots. It is further characterized by pain in the absence of a noxious stimulus and may be spontaneous or evoked by sensory stimuli such as light touch of the skin resulting in allodynia. An array of potential pain mechanisms may be causative in a given individual reflecting a combination of central and peripheral nervous system pathways. Deconstructing neuropathic pain phenotypes shows an interplay of genetics, plasticity, neuronal cognitive, autonomic and neuroimmunologic interactions and

 modulation. Hill and colleagues [152] recently reviewed the use of cannabis-based medicines (CBM) for pain.

According to Van Hecke and colleagues [153], a best estimate of the prevalence of pain with neuropathic characteristics in the general population is 6.9% and 10%, with more precise estimates for specific associated conditions such as postherpetic neuralgia (3.9 to 42.0/100,000 person-years (PY)), trigeminal neuralgia (12.6 to 28.9/100,000 PY), painful diabetic peripheral neuropathy (15.3 to 72.3/100,000 PY), and glossopharyngeal neuralgia (0.2 to 0.4/100,000 PY). Neuropathic pain ranked fifth among conditions cited by the Global Burden of Disease Study in 2010 for years lived with disability (YLD) [154], further accounting for loss of QoL, employment, and increased health costs. The global impact of neuropathic pain was exemplified by two studies, one in the UK [155] and one in Germany [156] that showed two- to three-fold higher levels of use of healthcare services in people with neuropathic pain than those without.

Most individuals with chronic neuropathic pain cite modest at best clinically relevant benefit from any one intervention [157] supporting the need for a multidisciplinary approach. Available pharmacologic interventions include topical lidocaine patches or low-concentration topical capsaicin [158], antidepressants like duloxetine and amitriptyline [159] and anti-epileptics including gabapentin or pregabalin [160]. The proportion of patients who achieve at least 50% relief is generally 10% to 25% more than with placebo alone [161].

Endocannabinoids serve as synaptic circuit breakers, regulating multiple physiological and pathological conditions including central and peripheral neuropathic pain. They use the brain's own cannabis-like substances, sharing the same molecular target as Δ^9-tetrahydrocannabinol, the main psychoactive component in cannabis. The benefit of cannabinoids in the management of chronic neuropathic pain is in their favorable modulation of cognitive and autonomic processing and brain signaling seen in chronic pain states, and their capacity to suppress behavioral responses to noxious

 stimulation and nociceptive processing [162]. The frontal-limbic distribution of CB receptors in the brain suggests that cannabinoids preferentially target the affective qualities of pain [163]. In addition, cannabinoids may attenuate low-grade inflammation, another postulate for the pathogenesis of neuropathic pain [164].

Aviram and Samuelly-Leichtag [165] conducted a systemic review and meta-analysis of all RCT published up to July 2015 on the efficacy of CBM compared to placebo for chronic neuropathic pain limiting inclusion to placebo-controlled trials, those with a cross-over or parallel design, and intervention groups that used any type of cannabis preparations included among them derivatives of THC, such as dronabinol, nabilone, Sativex®/nabiximols, cannabidiol, CT-3, ajulemic, acid, synthetic nitrogen analog of tetrahdrocannabinol (NIB), cannabinoid cigarettes/vaporizer, cannabinoid extract, fatty acid amide hydrolase-1 (FAAH1) inhibitor (PF-04457845), lovonantradol, and benzopyranoperidine (BPP). Control subjects received either placebo that was identical or an active weak treatment of an opioid or naproxen. Affected subjects included those suffering from chronic central and peripheral neuropathic pain. RCTs of healthy volunteers were excluded. Their analysis in over 1,300 patients showed a reduction in chronic pain (confidence intervals [CI] -0.78 to -0.43, P,0.0001) compared to placebo, with a decrease in pain scores of 2 points or 20% to 50%. The most prominent adverse effects were related to the CNS and gastrointestinal system. In spite of the promising findings of published reviews and meta-analyses of RCTs performed to date, there is a need for well-designed prospective studies to investigate the efficacy, tolerability, and safety of cannabinoids (herbal, plant-based, synthetic) compared to placebo or conventional drugs for chronic neuropathic pain using primary outcomes of pain relief of 50% or greater, self-reported patient global impressions of change, and tolerability; and secondary outcome measures of improved sleep, fatigue, psychological distress, health-related QoL.

A compelling reason to define the role of CBM for control of pain and legalization of their use in all states is to reduce physician and patient's reliance on opioid pharmacotherapy for the treatment of chronic neuropathic pain. In that regard, a recent examination of Medicare claims data showed

that use of prescription pain medications including opioids was significantly reduced in states following the implementation of medical cannabis laws [166].

HEADACHE

Headache is a major public health concern, with enormous individual and societal costs. Each year, about 47% of the population experience headache, including migraine (10%), tension-type headache (38%), and chronic daily headache (3%) [167]. Women are 2 to 3-fold more likely to experience a migraine headache and 1.25 times more likely to experience tension-type headache than men. Although cross-sectional data can be used to derive incidence rate estimates, they are better obtained from longitudinal studies [168]. Stewart and colleagues [169] estimated migraine incidence rates using reported age-at-onset data from a prevalence study admitting its inherent limitations. In Olmstead County, Minnesota, Stang and coworkers [170; 171] used linked medical records to identify those who sought medical care for migraine noting incidence rates for men and women under age 30 of 1.5- 2 and 3-6 per 1000 person/years respectively.

In the decade prior to GBD 2000, several epidemiologic studies noted varying estimates of migraine prevalence in the United States (US). Stewart and colleagues [169] conducted a population- based study in which a self-administered questionnaire sent to 15,000 households noted that 17.6% of females and 5.7% of males had one or more migraines per year. The prevalence of migraine varied considerably by age and was highest in both men and women between the ages of 35 to 45 years. Migraine prevalence was strongly associated with household income; prevalence in the lowest income group (less than $10,000) was more than 60% higher than in the two highest income groups (greater than or equal to $30,000). A projection to the U.S. population suggested that 8.7 million females and 2.6 million males suffer from migraine headache with moderate to severe disability. Of these, 3.4 million females and 1.1 million males experience one or more attacks per month. Females between ages 30 to 49 years from lower-income

households were at especially high risk of having migraines and were more likely than other groups to use emergency care services for their acute condition. Migraine ranked 19th as a leading cause of YLD representing 1.4% of the total causes of YLD in the 2001 World Health Organization annual report [172]. A special edition of Lancet that published the principal findings of GBD 2010 ranked migraine seventh in global YLD [154].

Vascular and neuronal mechanisms account for the characteristic mode of onset, duration, precipitating factors, and responsiveness to classes of medications [173]. The visual aura experienced by some migraineurs arises from cortical spreading depression (CSD), and that this neuronal event may also activate perivascular nerve afferents, leading to vasodilation and neurogenic inflammation of the meningeal blood vessels and, thus, throbbing pain. The involvement of parasympathetic pathways supplying the meninges leads to vasodilation and pain. As an acute attack progresses, sensory neurons in the trigeminal nucleus caudalis become sensitized, resulting in cutaneous allodynia. Triptan medications act at several points during the progression of a migraine attack, however, central sensitization may impact upon its effectiveness. In comparison, the trigeminal autonomic cephalgias (TAC) are characterized by short-lasting episodes of severe unilateral headaches that are associated with ipsilateral cranial autonomic symptoms [174]; the best known TAC is cluster headache. Other syndromes in this group include paroxysmal hemicrania, hemicrania continua, and short-lasting unilateral neuralgiform headache attacks that share a similar phenotype but may be distinguished by differences in attack frequency and duration. New daily persistent headache (NDPH) is an uncommon and under-recognized primary headache disorder that may resemble migraine or tension-type headache but is ultimately diagnosed by eliminating secondary mimics via serological, cerebrospinal fluid, and serologic studies, and an empiric trial of antibiotics for concomitant or preceding infection [175]. One other type of headache disorder, medication overuse headache (MOH) is a chronic headache that lasts ≥ 15 days/month and develops from primary migraine or tension-type headache, as a result of the interaction between overused therapeutic agents in a susceptible patient [176; 177]. Patients with chronic daily headache who overuse different types of analgesics are at risk

for developing MOH, and some can meet standard criteria for substance abuse. It is a common problem in tertiary headache centers, especially in patients with chronic migraine. Headache treatment ultimately depends on the underlying headache condition with most seeking initial benefit from non-steroidal anti-inflammatory drugs (NSAID) for mild headaches, triptans and ergotamine for more severe attacks, and prophylactic anti-depressants, calcium channel blockers, beta-blockers and non-pharmacological interventions such as cognitive-behavioral therapy or relaxation training for sufferers in remission.

Cannabis-based medicines and manipulation of the endocannabinoid system are positioned to impact neuronal and vascular components of the pathogenesis of migraine. Activation of CB_1 receptors in the CNS inhibit neurotransmitter release of gamma-amino butyric acid (GABA), glutamate, serotonin, dopamine, acetylcholine, noradrenaline, cholecystokinin, and D-aspartate at both inhibitory and excitatory synapses. It is one of the most abundant G-protein coupled receptors in both the PNS and CNS. CB_1 receptors are prominent not only in the anatomical pain pathways that include the periaqueductal gray (PAG) matter, rostral ventrolateral medulla, dorsal primary afferent and substantia gelatinosa spinal cord regions, spinal interneurons, and peripheral nerves/nociceptors, but also in other brain regions such as the amygdala, cerebral cortex, hippocampus, substantia nigra pars reticulata, basal ganglia, globus pallidus, and molecular layer of the cerebellum. The cardiopulmonary centers in the brainstem are sparsely populated with CB_1 receptors, which is why there is a lack of respiratory depression with the cannabinoids, as opposed to opiate receptors. The CB_2 receptors, primarily concentrated in the peripheral tissues, especially cells of the immune system, can also be found in lower concentrations in some brain regions including the PAG and some neuronal subpopulations: astrocytes, microglia, and oligodendrocytes. Anandamide (AEA), an endogenous ligand to the CB receptor, and other cannabinoid agonists have been shown to have inhibitory effects on serotonin type 3 (5HT3) receptors, which further suggests its role as an anti-emetic and in analgesia. Moreover,

the endocannabinoids are arachidonic acid derivatives synthesized on demand in the post-synaptic terminals from membrane phospholipid precursors in response to cellular metabolic needs, and there appears to be cross-talk between the eicosanoid and endocannabinoid pathways. CB_1receptor mediated anti-inflammatory effects of cannabinoids are suspected to be secondary to inhibition of arachidonic acid conversion by cyclooxygenase, although CB_2receptor activation, which induces immunosuppression, also reduces inflammation.

Extraordinary progress has been achieved in the role of the endocannabinoid system in experimental models of migraine. Variations in the CB_1gene predispose to migraine that relate to peripheral trigeminovascular activation. In animal models, endogenous cannabinoids have an inhibitory effect on trigeminovascular activation through the CB_1receptor suggesting a potential role of CB_1in human migraine [178]. Endocannabinoid levels are reduced in the platelets of migraine patients, and CSD, believed to be a neuronal mechanism underlying migraine aura and subsequent pain, is suppressed by activation of CB_1receptors in a murine model of migraine. [179]. Systemic nitroglycerin (NTG) which produces spontaneous-like migraine attacks in migraine sufferers and induces hyperalgesia in the rats 4 hours after its administration, appears to be modulated by the endocannabinoid system. Anandamide is tonically released to modulate the trigeminovascular system and inhibits trigeminovascular-mediated nociception [180; 181]. The antinociceptive effects of AEA are not clearly understood however the antinociceptive effects of Δ9-THC are attenuated after spinal transection suggesting that cannabinoids produce antinociception through multiple mechanisms at supraspinal and spinal levels of the central nervous system [182]. Triptans, the most effective abortive treatments for migraine and cluster headaches, act through agonist effects on 5HT1B/1D receptors on the nerve endings in cranial blood vessels [183], as well as brainstem regions, including the peri-aqueductal gray (PAG) [184] resulting in decreased release of pro-inflammatory neuropeptides such as substance P and attenuation of dural

nociceptive responses. Since 5HT1B/1D antagonists inhibit the CB_1 modulation of nociceptive trigeminovascualr signals, triptans may induce their anti-migraine effects by activating endocannabinoid-containing neurons in the PAG.

Although no RCT have been conducted to demonstrate the effects of CBM in patients with headache, there is emerging literature suggesting that it may be a promising therapeutic agent in a variety of clinical headache disorders. Rhyne and colleagues [185] described the effects of medical marijuana on the monthly frequency of migraine headache in a retrospective review of two medical marijuana specialty clinics in Colorado between 2010 and 2014 noting a decrease in the frequency of migraines from 10.4 to 4.6 headaches per month ($p < 0.0001$) with the use of medical marijuana. Positive effects were reported in 39.7% of patients, most commonly prevention of migraine headache and decreased frequency of migraine headache (19.8%), or aborted migraine headache (11.6%).

A small case series of cannabis use for patients with pain included 3 subjects with chronic headaches that were relieved by smoking cannabis, with results similar or superior to ergotamine and aspirin [186] Another small case series of 3 patients reported that abrupt cessation of chronic daily marijuana smoking was followed by migraine attacks, while subsequent remission of headaches was seen with resumption of episodic marijuana use in 1 of the patients [187]. A case of a migraineur who had failed standard medical therapy, and ultimately received relief with small doses of smoked marijuana was reported [133]. Baron [188] cited his experience with multiple patients with chronic migraine, and a similar history of failing all standard medical therapy, but receiving a significant positive response to smoked cannabis or synthetic cannabinoids. Robbins and coworkers [189] described a patient with cluster headache who was refractory to multiple acute and preventive medications but successfully aborted his attacks with recreational marijuana use; subsequent use of dronabinol provided equally effective pain relief. The beneficial effect was believed to be related to the high concentration of cannabinoid receptors in the hypothalamus, implicated

as a site of dysfunction in neuroimaging studies of patients with cluster headache. Similarly, Leroux and coworkers [190] examined the frequency of cannabis use in 139 cluster headache patients, and the reported effects on attacks noting that among 27 (19.4%) patients who tried cannabis to treat attacks, 25.9% reported some efficacy, 51.8% variable or uncertain effects, and 22.3% negative effects. Evans and Ramadan [191] described a 38-year-old woman with pseudotumor cerebri with recurring headaches and bilateral disc edema who noticed that if she smoked a marijuana cigarette when the headache was severe, it resolved within 5 minutes without recurrence that day.

Given the diversity of primary headache syndromes and the wealth of experimental and early human data on the salutary benefit of CBM in treatment, it is certain that investigators will be testing the potential benefits of CBM in the treatment of migraines and other primary headache disorders. For the present time, physicians with refractory cases ought not be deterred from considering such treatment under carefully monitored circumstances.

CANCER SYMPTOM MANAGEMENT

Cancer Induced Nausea and Vomiting

Early studies demonstrated the utility of cannabinoids in the management of chemotherapy-induced nausea and vomiting (CINV) [192]. Among 30 randomized comparisons of cannabis with placebo or antiemetic in a total of 1366 patients, oral nabilone, oral dronabinol, and intramuscular levonantradol were more effective antiemetic than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride. There were associated potential beneficial side effects including sedation or drowsiness, and euphoria [193]. However, no smoked cannabis trials were included. In crossover trials, patients preferred cannabinoids for future chemotherapy cycles.

A subsequent analysis of seventy-two controlled studies evaluating the therapeutic effects of cannabinoids [194] compared nabilone to placebo or available antiemetic in over 600 patients with a variety of malignant diagnoses, noting that nabilone was superior to prochlorperazine, domperidone, and alizapride, with patients clearly favoring nabilone for continuous clinical use. A small pilot, randomized, double-blind, placebo-controlled phase II trial investigating whole-plant cannabis-based nabiximols added to standard antiemetics in the treatment of CINV [195] found cannabis-based medicine containing THC and cannabidiol taken in conjunction with standard therapies provided better protection against CINV compared with placebo.

Two trials evaluated the efficacy of smoked marijuana to alleviate nausea and vomiting accompanying cancer chemotherapy. In the first study reported by Chang and colleagues [196], 15 patients with osteogenic sarcoma receiving high-dose methotrexate chemotherapy were studied in a randomized, double-blind, placebo-controlled trial of oral and smoked THC as an antiemetic. Each patient served as his or her own control. Fourteen of 15 patients had a reduction in nausea and vomiting on THC as compared to placebo. Δ^9-tetrahydrocannabinol was significantly more effective than placebo in reducing the number of vomiting and retching episodes, degree of nausea, duration of nausea, and volume of emesis ($P < 0.001$). There was a 72% incidence of nausea and vomiting on placebo. When plasma THC concentrations measured less than 5.0 ng/mL, 5.0 to 10.0 ng/mL, and greater than 10.0 ng/mL, the incidences of nausea and vomiting were 44%, 21%, and 6%, respectively. Δ^9-tetrahydrocannabinol had significant antiemetic properties when compared with placebo in patients receiving high-dose methotrexate

The second study reported by Chang and colleagues [197] was a randomized, double blind, placebo-controlled trial of oral and smoked Δ^9-tetrahydrocannabinol performed in eight patients with resected soft tissue sarcomas who received adjuvant Adriamycin and cyclophosphamide chemotherapy. Each patient served as his own control. Δ^9-tetrahydrocannabinol, in comparison to placebo, did not significantly reduce the number of vomiting and retching episodes, volume of emesis, degree of

nausea, or duration of nausea in conjunction with Adriamycin and cyclophosphamide suggesting that its antiemetic effects were chemotherapy specific.

Anorexia and Cachexia

There are very few successful approaches to avert cancer-related anorexia and cachexia (CACS). An RCT of 54 adults with advanced cancer treated with oral THC experienced stimulation of appetite and retardation of chronic weight loss with an average weight gain of 1.25 pounds compared to a loss of 21.25 pounds on placebo [198].

Jatoi and colleagues [199] studied whether dronabinol administered alone or with megestrol acetate was more, less, or equal in efficacy to single-agent megestrol acetate for palliating cancer-associated anorexia. Four hundred sixty-nine assessable advanced cancer patients were randomized to (1) oral megestrol acetate 800 mg/d liquid suspension plus placebo, (2) oral dronabinol 2.5 mg twice a day plus placebo, or (3) both agents. Eligible patients acknowledged that loss of appetite or weight was a problem and reported the loss of 5 pounds or more during 2 months and/or a daily intake of less than 20 calories/kg of body weight. Groups were comparable at baseline in age, sex, tumor type, weight loss, and performance status. A greater percentage of megestrol acetate-treated patients reported appetite improvement and weight gain compared with dronabinol-treated patients: 75% versus 49% (P = .0001) for appetite and 11% versus 3% (P = .02) for > or = 10% baseline weight gain. Combination treatment resulted in no significant differences in appetite or weight compared with megestrol acetate alone. A Functional Assessment of Anorexia/Cachexia Therapy questionnaire, which emphasizes anorexia-related questions, demonstrated an improvement in quality of life (QOL) among megestrol acetate-treated and combination-treated patients. A single-item Uniscale, a global QOL instrument, found comparable scores. Toxicity was also comparable, with the exception of an increased incidence of impotence among men who received megestrol acetate. Thus, in the doses and schedules so studied,

megestrol acetate provided superior anorexia palliation among advanced cancer patients compared with dronabinol alone. Combination therapy did not appear to confer additional benefit.

More recently, the Cannabis-in-Cachexia Study Group [200] compared the effects of cannabis extract (CE) and THC on appetite and quality of life QOL in patients with cancer-related anorexia-cachexia syndrome. Two-hundred forty-three adult patients with advanced cancer, weight loss (> or = 5% over 6 months) and CACS were randomly assigned to receive CE (standardized for 2.5 mg THC and 1 mg cannabidiol) or THC (2.5 mg) twice daily for 6 weeks. Appetite, mood, and nausea were monitored daily and QOL was assessed. At baseline, groups were comparable for age, sex, weight loss, antineoplastic treatment, appetite, and QOL. Increased appetite was reported by 73% and 58% of patients receiving CE and THC, respectively, without a statistically significant difference indicating equal efficacy. Moreover, cannabis extract at the oral dose administered was well tolerated.

CANCER PAIN

Cancer pain results from inflammation, mechanical invasion of bone or other pain-sensitive structures, and nerve injury. It is severe, persistent, and often refractory to treatment with opioids. It is one of the most common symptoms in cancer patients, especially in advanced disease. It occurs in a significant proportion of patients during diagnostic and therapeutic procedures, and in some, pain may be the first symptom of cancer. The causes of pain in cancer patients are often multifactorial including direct and indirect cancer effects, anticancer therapy and co-morbidities. Moreover, pain in cancer patients has mixed pathophysiology including both nociceptive and neuropathic components, especially in patients with bone metastases. Recognition of pain and its appropriate assessment and treatment may significantly improve in patients and families' quality of life.

Schmidt (Schmidt BL. The neurobiology of cancer pain. Neuroscientist 2014; 20:546-562) described an attractive strategy for the treatment of

cancer pain exploiting the endogenous analgesic system in the cancer microenvironment with cannabinoid and opioids. Preclinical studies suggest that the peripheral endocannabinoid system is a promising target for managing bone cancer pain [201] as a local peripheral increase of 2-arachidonoyl glycerol (2AG) decreases mechanical hyperalgesia secondary to fibrosarcoma inoculated into the calcaneus bone. These preclinical studies reinforce that cannabinoids remain a good target for control of cancer pain and have shown promise in clinical studies (Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 2012; 13: 438–49).

Van den Beuken-Van Everdingen and colleagues [202] performed a meta-analysis of the prevalence of cancer pain in published literature from 2005 to 2014, noting that among 122 studies so selected, the prevalence of pain was 39.3% after curative treatment; 55.0% during anticancer treatment; and 66.4% in advanced, metastatic, or terminal disease. Moderate to severe pain (numerical rating scale score $\geq$ 5) was reported by 38.0% of all patients. The authors concluded that despite increased attention on assessment and management, pain continues to be a prevalent symptom in cancer. The authors concluded that in the decade ahead, it was incumbent upon physicians to develop and implement effective interventions in cancer pain, hence the importance of integrating medical cannabis into the available modalities of pain management at all stages of cancer care.

Two studies on the impact of oral THC on cancer pain used single-dose analgesic methods to study the relative efficacy of a 5, 10, 15 and 20 mg dose of oral THC over a 6-hour period [203; 204] noting significantly superior pain relief compared to placebo especially at 15 mg which was well-tolerated despite sedative effects and mild mental clouding. A 10 mg dose of THC was comparable in its analgesic effects to 60 mg of codeine with only mild sedation. Such patients incidentally had improved mood, sense of well-being, and reduced anxiety.

Johnson and colleagues [205] reported their experience in the treatment of intractable cancer pain employing whole-plant extract cannabis in 177 patients who experienced inadequate analgesia despite chronic opioid

dosing. Patients were randomized to a tetrahydrocannabinol: cannabidiol (THC: CBD) extract (n = 60), THC extract (n = 58), or placebo (n = 59). A numerical rating scale score showed statistically significance in favor of THC: CBD compared with placebo (improvement of - 1.37 vs. - 0.69), whereas the THC group showed a no significant change (- 1.01 vs. - 0.69). Twice as many patients taking THC: CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 [43%] vs. 12 [21%]). Hence, THC: CBD extract was highly efficacious for relief of pain in patients with advanced cancer pain not fully relieved by strong opioids.

ANTI-CANCER EFFECTS

Extraordinary advances have occurred in the pharmacologic importance of synthetic and endogenous cannabinoids not only for their anti-palliative effects, but also as promising anti-cancer agents through their *in vitro* as well as *in vivo* anti-proliferative and anti-angiocentric properties [206]. Cannabinoids regulate key cell signaling pathways that are involved in cell survival, invasion, angiogenesis, metastasis, etc. There is more focus on CB_1 and CB_2, the two cannabinoid receptors that are activated by most of the cannabinoids. In a striking series of *in vitro* murine experiments, Munsor and colleagues demonstrated the antiproliferative effects of cannabinoids more than four decades ago [207] in in experimental Lewis lung adenocarcinoma and Friend leukemia virus-induced splenomegaly with the oral administration of Δ^9-THC, Δ^8-THC, and cannabinol but not cannabidiol. Mice treated for 20 consecutive days with Δ^8-THC and cannabinol had reduced primary tumor size. Δ^9-THC, Δ^8-THC, and cannabinol-treated mice increased their mean survival time proportionate to the dose (36% at 100 mg/kg, 25% at 200 mg/kg, and 27% at 50 mg/kg, respectively).

Nikan and colleagues [208] reviewed the suppressive effects of activation of the endocannabinoid system on tumor evolution and progression. The application of multiple cannabinoid or cannabis-derived

compounds reduces tumor size through decrease of cell proliferation or induction of cell cycle arrest and apoptosis. Cannabinoid compounds have been shown to inhibit the growth of tumor cells in culture and animal models by modulating key cell-signaling pathways [209].

The modulation of endocannabinoid system by inhibition of fatty acid amide hydrolase (FAAH), the enzyme, which metabolized endocannabinoids, or application of multiple cannabinoid or cannabis-derived compounds, may be appropriate for the treatment of several cancer subtypes. According to Chakravarti and colleagues [210], cannabinoid compounds may have the potential to regulate key cell signaling pathways that are involved in cell survival, invasion, angiogenesis, and metastasis, accordingly, there is a focus on CB_1 and CB_2, the two cannabinoid receptors which are activated by most of the cannabinoids. Receptor activation affects Ca^{2+} and K^+ channels, modulating adenyl cyclase and cyclic AMP (c-AMP) levels in most tissues and models, regulating members of the mitogen activated protein kinase family (MAPK) including extracellular signal regulated kinase-1 and -2 (ERK1/2), p38, MAPK and c-Jun N terminal kinase (JNK).

One important by-product of energy metabolism, the reactive oxygen species (ROS), produced from mitochondria and consists of H_2O_2, superoxide O^{2-}, and hydroxyl radical O^{2-}, have been associated with triggering of apoptosis [211]. CBD modulates ERK and ROS pathways, which lead to down-regulation of Id-1 expression. Id-1, an inhibitor of basic helix-loop-helix transcription factors, was recently shown to be a key regulator of the metastatic potential of breast cancer cells [212]. Arachidonoyl cyclopropamide (ACPA) or GW405833 (GW) induce AMPK mediated autophagy in pancreatic adenocarcinoma cells that is strictly related to the inhibition of energy metabolism through a ROS-dependent increase of the AMP/ATP ratio. The combination of cannabinoids and gemcitabine, a nucleoside analogue used in cancer chemotherapy, synergistically inhibit pancreatic adenocarcinoma cell growth by a ROS-mediated autophagy induction without affecting normal fibroblasts [213].

Cannabidiol induces endoplasmic reticulum stress mediated cell death of MDA-MB231 breast cancer cells, with the coexistence of autophagy and

apoptosis. One recently published report [214] showed that Δ^9-THC and Δ^8-THC inhibited mitochondrial oxygen consumption rate via receptor independent manner in oral cancer cells.

Despite impressive *in vitro* and animal model findings of the potential antitumor effects of cannabinoids, there is yet no basis for the claim that highly concentrated cannabis extracts or oils will cure cancer, as there have not been robust human studies investigating cannabis as anticancer agents in lieu of conventional therapy in a randomized control trial. Nonetheless, the addition of cannabinoid-based preparations to standard chemotherapy should not be discontinued by treating oncologists.

Nor has there been convincing evidence of cannabis and enhanced cancer risk. Among Kaiser Permanente healthcare members seen between 1979 and 1985 and followed through 1993, men aged 15-49 years, there was no association between marijuana use and cancer in over 50,000 person-years of follow-up of men who only smoked marijuana [215].

A population-based case-controlled study of the association of marijuana use and risk of lung and upper aerodigestive tract cancers [216] found no association of cancer with marijuana use among 1,212 incident cancer cases and 1,040 cancer-free matched controls.

The New England Journal of Medicine presented a case of a 68-year-old woman with metastatic breast cancer seeking medicinal marijuana for symptom management [217]. Readers were asked to participate in a poll the results of which were published in a subsequent article. The authors remarked that they were surprised to learn that 76% voted in favor of the use of marijuana for medicinal purposes even though its use was illegal. Hence, there is increased and concerted support and education is warranted in the coming years to make medicinal marijuana an available option for an increasing number of patients who will benefit from its use in the management of cancer.

LEGALIZATION OF MEDICAL CANNABIS

PHYSICIANS POINTS OF VIEW

While the medical community and legislators debate the merits of marijuana reform, legalization is advancing across the United States. While still prohibited under federal law, medical marijuana is now legal in 29 states, and in 8 states, medical cannabis can be purchased by anyone older than 21 years. Federal support of state cannabis laws is critical for the millions of patients who require the medication. Despite the contentious divisions in American politics, marijuana legalization has found bipartisan support. The government's own statistics explain the decades-long, steady shift in public opinion. Every year, the US makes 575,000 arrests for marijuana possession alone, which is greater than the number of arrests for all violent crimes combined [218]. Blacks are four times more likely than Whites to be arrested for marijuana possession despite similar usage rates between the two groups [219]. Enforcement of marijuana laws disproportionately affects our nation's poor communities of color, contributing to the crisis of mass incarceration. The war on marijuana exacerbates poverty and has the potential to reduce the access to health care. The unjust prohibition of marijuana has done more damage to public health than has abuse of the marijuana itself.

The case for decriminalization of marijuana and legalization of medical cannabis among physicians, according to Nathan and colleagues [220] is unsettled. While many physicians who oppose legalization of medical cannabis continue to support legalization to decriminalize marijuana, there are many serious problems with that position. Decriminalization prevents the government from regulating product labeling and purity, leaving marijuana vulnerable to contamination and adulteration. Without knowing its potency, consumers are unable to use it responsibly. Decriminalization still leaves marijuana in the hands of drug dealers and not responsible vendors, and prosecutes marijuana growers and sellers thereby constricting the supply chain and driving up its price, sustaining it as a lucrative untaxed illegal product and providing market incentive for more competitive and violent procurement.

Contrary to the policy of alcohol prohibition that historically was repealed after only 13 years, physicians have advocated for effective regulation. Doctors for Cannabis Regulation (DFCR), a national organization of physicians dedicated to the legalization and regulation of the adult use of marijuana published a declaration of principles for medical cannabis regulation [221] citing that the vast majority of adults are unharmed by the responsible use of cannabis [222] and the lack of evidence that cannabis is a gateway for later use of more harmful drugs [223; 224]. Legalization encourages honesty in patient-doctor communication about cannabis use [225]. Properly structured, tax revenues from cannabis sales can fund research, education, substance abuse treatment programs, and community reinvestment [226]. Legalization would reduce the disproportionate impact of the criminal justice system on low-income and minority citizens [227]. Regulation benefits public health by enabling government oversight of the production, testing, labelling, distribution, and sale of cannabis [228]. An end to prohibition creates the legal distinction between underage and adult use, differentiating its use by responsible adults.

Concerned physicians advocate cannabis packaging and advertising that targets adults and prohibits underage use by minors enforced by child-resistant packaging and strong penalties for those who enable its use in children. Informed physicians may disagree about the specifics of good

regulation, but we cannot abstain from the discussion. As cannabis growers and pharmaceutical experts advise lawmakers on its regulation, there is an increasing need for physicians to do so as well.

MEDICAL CANNABIS COULD SOLVE THE OPIOID EPIDEMIC

Pop stars hospitalized and others dying of opioid overdoses has refocused the nation on an epidemic of wide-ranging proportion that threatens the fabric of our values, and highlighting the disparity in the risk of recreation or medical cannabis use. Prescription opioid overdoses resulted in the deaths of more than 165,000 Americans between 1999 and 2014, with an associated health and social costs of $55 billion annually. Over the past two decades, opioid analgesics have become a leading pain management strategy and dispensing has tripled [229]. In parallel, the incidence of opioid use disorder and opioid overdoses have both dramatically increased [230]. To reduce these harms, patient groups, clinicians, and policymakers have called for new strategies to address pain management and reduce use of opioid analgesics.

Bachhuber and colleagues [231] recently reviewed the state of research in chronic pain including those who might benefit from medical cannabis instead of opioids. The 2017 landmark study of the National Academies of Science, Engineering, and Medicine finding of the substantial efficacy of cannabis' in treating chronic pain [232] has led to an important and rapidly expanding strategy to substituting medical cannabis for opioid medications in an effort to address the opioid epidemic.

Several road blocks remain to make cannabis a realistic and medically accepted alternative to opioids. The first is the gaps in research demonstrating unequivocal benefit in pain management using RCTs which continue to face numerous hurdles because of the Schedule 1 status of cannabis. Although the Drug Enforcement Administration (DEA) announced policy changes to expand the number of cannabis manufacturers, currently only one entity is authorized to produce and supply cannabis to

U.S. researchers [233]. The cannabis products available for research are limited in scope and not necessarily comparable to cannabis products available in state dispensaries. Even when products are obtained for research, they typically must be dispensed in a directly observed setting. Over the past several decades, only six US clinical trials have administered cannabis to examine its effect on pain and they all occurred in tightly controlled human laboratory settings at short distances and with small sample sizes of less than 100 participants [234-238; 203]. Notwithstanding, enrolling cannabis-naïve participants in a RCT could introduce significant biases due to its already broad use and the likelihood of participants to be invested in a positive outcome. Others might not be motivated to enroll in a RCT because of cannabis' widespread availability outside of the trial. Given current limitations of interventional research, observational studies are an appealing alternative. Longitudinal cohort studies of patient-reported pain outcomes are feasible, and even intensive assessments of pain have not been found to affect participants' responses [239; 240]. While longitudinal cohort studies that simply compare those who use medical cannabis to those who do not would be inescapably confounded, more complex designs and analyses could potentially come closer to estimating causation [241]. The management of treatment-resistant chronic pain with medical cannabis has shown promise. Haroutounian and colleagues [242] conducted an open-label, prospective cohort of 274 participants in which the primary outcome was a change in the pain symptom score and an important secondary outcomes were pain severity, interference, social and emotionally disability scores, and change in opioid consumption. At six month follow-up, there were significant changes (p < 0.001) in pain symptoms, severity and interference scores, together with social and emotional disability scores, and opioid consumption improved by 44% without serious adverse effects. While each of these analyses has limitations, users of medical cannabis were less likely to suffer than a general population of chronic pain patients and the treatment allowed a significant proportion of patients to discontinue opioid use.

While experimental clinical trials provide the most definitive proof on any cause and effect relation between medical cannabis and reduced opioid

use, such studies are difficult because its Schedule I substance status decrees it as having no currently accepted medical use and a high potential for abuse. Other countries have similar restrictions that pose challenges for researchers to legally obtain cannabis or to get approval for clinical trials. Nonetheless, such trials are also a necessary next step because they would help determine safety. Thus, states with legalized medical cannabis need to be guided toward a policy on the ways that cannabis can be researched and accessed by the scientific community.

EPIDEMIOLOGICAL TRENDS IN CANNABIS USE

Cerda and colleagues [243] used the second wave of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a national survey of adults aged 18+ (n = 34,653), to measure past-year cannabis use, abuse, and dependence. Residents of states with medical marijuana laws had higher odds of marijuana use (OR: 1.92; 95% CI: 1.49-2.47), however, marijuana abuse/dependence was not more prevalent among marijuana users in these states (OR: 1.03; 95% CI: 0.67-1.60). There were four possible explanations for these findings. First, state-level community norms more supportive of marijuana use may contribute to the legalization of medical marijuana and to higher rates of marijuana use. The passage of state medical marijuana laws may reflect underlying state-level community norms, especially when such legislation is passed by voter referenda. Medical marijuana laws passed in state legislatures by wide margins of votes appear to reflect an underlying high level of support for such legislation prior to their enactment, as well as the absence of a strong and vocal minority opposition. Second, the enactment of medical marijuana laws could lead to a change in community attitudes on both medical and non-medical marijuana use, including reduced disapproval and perceived riskiness of use, which could subsequently influence marijuana use and abuse/dependence. Third, medical endorsement of its use for medical purposes appears to play a role in spite of the lack of medical consensus on the indications for its use by many professionals. Thus, it is incumbent on physicians to deliver a clear

message to the public. Fourth, marijuana availability in states where it is legal can lead to greater commercial promotion and availability of the substance for recreational purposes, which may contribute to greater illicit use of marijuana. State legalization of medical marijuana may also be associated with potential health, economic, and social gains. This study highlights the key role that macro-level factors, such as policy changes and community norms about substance use, play in shaping marijuana use. Future studies are needed on the consequences of increased marijuana use, as well as on the particular impact of medical marijuana legalization on youth, who bear a disproportionate burden of marijuana-related disorders and maybe vulnerable to the advertising effects of other substances such as tobacco. In particular, future studies in the US and elsewhere should compare trends in community norms, marijuana use and abuse/dependence before and after the legalization of marijuana, to understand the relative contribution of medical marijuana legalization and community norms on changes in marijuana use and abuse/dependence.

Stith and colleagues [244] conducted a pragmatic historical cohort study measuring the effect of enrollment in a state-authorized Medical Cannabis Program (MCP) on scheduled II-V drug prescription patterns among patients with chronic pain. Legal access to cannabis may reduce the use of multiple classes of dangerous scheduled II-V drug prescription medications in certain patient populations.

Little is known about whether medical marijuana is being used clinically to any significant degree in senior citizens eligible for Medicare Part D. Using data on all prescriptions filled by Medicare Part D enrollees from 2010 to 2013, Bradford and Bradford [245] found that the use of prescription drugs for which marijuana could serve as a clinical alternative fell significantly, once a medical marijuana law was implemented. With national overall reductions in Medicare programs estimated at $165.2 million per year in 2013 in enrollee spending in states with implemented medical marijuana laws, the availability of medical marijuana may have a significant effect on prescribing patterns and spending among Medicare Part D beneficiaries.

Chapter 9

PRESCRIBING ALGORITHMS FOR MEDICAL CANNABIS

ROUTES OF ADMINISTRATION

Common modes of administration and formulations are inhalation by vaporization (herbal cannabis, resin, concentrates); oral ingestion (prescription cannabinoids, edibles, and tinctures); oro-muscosal or sublingual (lollipops, lozenges, nabiximols), and topic or rectal administration (herbal cannabis, resin, concentrates).

Vaporizing is the preferred route for starting therapy. Among a survey of 6,883 cannabis users, vaporizing, compared with smoking, was associated with fewer respiratory symptoms (Earlywine and Barnwell, 2007). Analysis of vapor from a vaporizer recovered 89.1% THC and 9.5% smoke toxins compared to 10.8% THC and 87% smoke toxins when smoked from a pipe (Chemic laboratories, 2003). The general approach to cannabis initiation is 'start low, go slow, and stay low'. For cannabis inhalation, patients should start with 1 inhalation and wait 15 min. Then, they may increase by 1 inhalation every 15–30 min until desired symptom control has been achieved. Higher THC concentrations of herbal cannabis may allow

 utilization of lower amounts. Patients should titrate accordingly to avoid adverse events. THC-mediated side effects such as fatigue, tachycardia and dizziness are avoidable when starting dose is low and titration is slow. Slow upward dose titration promotes tolerance to psychoactive sequelae of THC, which is especially important for naïve users. Medical cannabis patients, in contrast to recreational users, frequently use CBD-predominant chemovars with the smallest amount of THC to get the greatest improvement in symptom control, function, and quality of life, with fewest adverse events. The attainment of euphoric effects is not required to attain symptom control. For chronic conditions and symptoms, long acting oral preparations are the mainstay of treatment. Vaporization can be utilized as an add-on technique for episodic exacerbations of symptoms. CBD can balance THC side effects, especially in daytime use, or when driving is required. Cannabis should be stored in a safe place, or lock box in the home. Physicians should clearly communicate the potential risks and safety of cannabis, no differently than with any psychoactive medication. A standard treatment agreement form should be used for medical-legal purposes.[1] Patients should keep a symptom inventory chart indicating response or efficacy for each cannabis product for each symptom as an aid for physicians in determining treatment response to cannabis in follow up visits.

DRUG INTERACTIONS AND ADVERSE SIDE EFFECTS

Although states have legalized marijuana for personal, recreational use or medicinal use, physicians need to remember that medical cannabis is still a Schedule 1 drug according to the Drug Enforcement Agency (DEA), and that its use by patients holds inherent risk [246]. Patients certified for medical cannabis should be informed about the potential adverse side effects, such as acute impairment of memory, coordination and judgment,

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[1] Retrieved from, https://www.drcarolinemaccallum.com/cannabis-resources/ .

and possible chronic effects, such as cannabis use disorder, cognitive impairment, and chronic bronchitis [247]. Marijuana itself has low to moderate dependent potential; the active dose is very far below the lethal dose. Common adverse side effects include reddened eyes, dizziness, altered sense of time, reduced tear flow, anxiety, changes in visual perception, dry mouth, slow pupillary responses, sedation, cough, ataxia and dysphoria. THC and CBD are metabolized by CYP3A4 and CYP2C9. THC is a CYP1A2 inducer, and can theoretically decrease serum concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine. As a potent inhibitor of CYP3A4 and CYP2D6, CBD may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin, but not pravastatin or rosuvastatin). As CYP2D6 metabolizes many antidepressants, CBD may increase serum concentrations of selective serotonin reuptake inhibitors, tricyclic antidepressant, antipsychotic, or beta blocker, and opioid medications. Cannabis has additive CNS depressant effects with alcohol, barbiturates and benzodiazepines. Contraindications to the use of cannabis include acute psychosis and other unstable psychiatric conditions. It is relatively contraindicated in severe cardiovascular, immunological, liver, or kidney disease. Medical cannabis use in adolescence, but not in adulthood, may increase psychotic symptoms later in life. Although medical cannabis acts as an anxiolytic in low doses, higher doses can be anxiogenic and elicit panic reactions. Chronic use may increase the risk of depression, however that risk is weak.

EXEMPLARY FORMULATORY PRODUCTS

Most dispensaries will provide a range of products and delivery systems for medical cannabis with a ratio (THC:CBD) titrated to the strength needed

 for maximal clinical benefit depending upon the diagnosis. The available product formulations will vary from one dispensary to another. Vireo Spectrum™ dispensaries in New York provide an exemplary range of medical cannabis products with varying THC:CBD concentrations (Table 2).

PRESCRIBING ALGORITHM

Patients should be counseled by the dispensing pharmacist according to a simple algorithm based upon the patient's diagnosis, age, weight and concomitant medical conditions that may impact the product, dose and route of therapy as for example lung disease that would favor oral solutions or capsules over vapor, or swallowing difficulties making vaporization the preferred route of delivery over oral solutions or capsules. Patients are advised to start with the lowest concentration of 2.mg of THC and 2.5 mg of CBD available in green capsules, taking the first capsule four hours before bedtime to observe the effects overnight and into the next day after awakening. If the medication is still working the next morning, they are advised to allow the clinical effects to wear off before taking another dose. If a single capsule does not offer maximal clinical benefit, they are advised to increase the dose the next evening to 2 capsules. Whichever dose is maximally desirable is continued for 3 to 4 days two to three times daily and at bedtime. The move to a higher concentration of yellow tablets composed of 4.3 mg THC and 0.7 mg CBD, or red tablets composed of 4.75 mg THC and 0.25 mg CBD, should occur under the careful guidance of the prescribing physician and administering pharmacist. Similar strategies are followed for the oral solution and cartridge-delivered vaporization delivery systems of varying THC:CBD potency (Figure 5). Whether in capsule, oral solution or vaporization form, beginning with the lowest ratio of THC:CBD and slowly increasing the ratio and dosage, will achieve the desired clinical benefit with the least undesirable side effects.

Table 2. Dispensary Formulary of Medical Cannabis Products[*]

THC:CBD 19:1			
Product	**THC**[*]	**CBD**[*]	**Doses**[**]
Capsules	4.75 mg/capsule	0.25 mg/ capsule	30
Prefilled Vaporizer Cartridge, 0.5 mL Cartridge	237.5 mg/cartridge	12.5 mg/ cartridge	100
Oral Solution, 25 mL Bottle	23.75 mg/mL	1.25 mg/ mL	125
THC:CBD 6:1			
Product	**THC**[*]	**CBD**[*]	**Doses**[**]
Capsules	4.3 mg/capsule	0.7 mg/capsule	30
Prefilled Vaporizer Cartridge, 0.5 mL Cartridge	214 mg/cartridge	36 mg/cartridge	100
Oral Solution, 25 mL Bottle	24 mg/mL	4 mg/mL	125
THC:CBD 1:1			
Product	**THC**[*]	**CBD**[*]	**Doses**[**]
Capsules	2.5 mg/capsule	2.5 mg/capsule	30
Prefilled Vaporizer Cartridge, 0.5 mL Cartridge	125 mg/cartridge	125 mg/cartridge	100
Oral Solution, 25 mL Bottle	25 mg/mL	25 mg/mL	125

Figure 6. Algorithm for Prescribing Medical Cannabis[*]
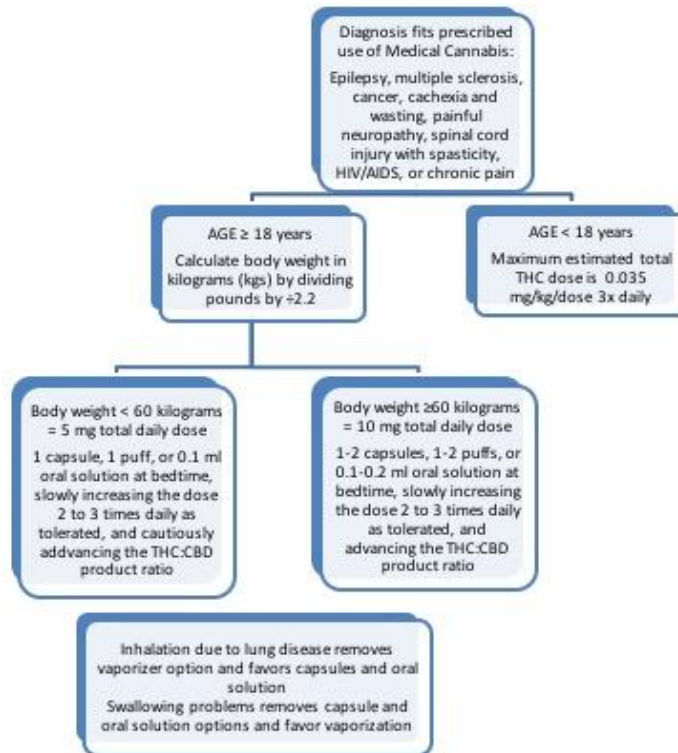
[*] Adapted from Vireo at VireoHealth.com/NY.

Chapter 10

FRAMING PUBLIC HEALTH POLICY OF MEDICAL CANNABIS[1]

Political ideology, conflicting medical evidence and opinions and media attention have all impacted the formulation of public health policy of medical cannabis. Recognizing that caregivers and patients look for treatment options for unmet medical needs, in one rare instance, the FDA recently approved the purified cannabidiol Epidolex®, produced by GW Pharmaceuticals for the treatment of refractory seizure disorders in children age ≥2 years due to severe myoclonic epilepsy of infancy, and Lennox-Gastaut syndrome[2]. There are pathways for expanded access and compassionate use of cannabinoids in the treatment of refractory seizures due to infantile spasms and tuberous sclerosis complex by the same pharmaceutical manufacturer[3]. Patients with glaucoma, AIDS wasting syndrome, neuropathic pain, cancer, MS, chemotherapy-induced nausea, and other seizure disorders, for which clinical trials have shown efficacy of medical cannabis, await FDA approval. However, failing to legalize medical cannabis, the US DEA, which continues to list medical cannabis as a

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[1] Emelie Philips MPH, NYU College of Global Public Health assisted in the research and preparation of this chapter.

[2] Retrieved from, https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421163.htm.

[3] Retrieved from, http://www.gwpharm.com/healthcare-professionals/research-trials/epilepsy.

Schedule 1 agent, lists marijuana as an agent without medical use[4], adds to the difficulty of states' legislators to implement regulations governing the dispensation of registered medical cannabis by credentialed health care providers to patients with certified needs [248, 249]. The diversity in the way that states have regulated medical cannabis as regards to the permissible amount an individual can possess, as well as differences in the pathways for provider, dispensary and patient registration and certification to be eligible for participation, and perceptions surrounding its legitimate use, collectively add to the complexity in forming a unified public health policy.

FRAMING PUBLIC HEALTH POLICY

The past several decades have witnessed a dramatic increase in societal interest in not only preventing due to contracting chronic diseases, but in recognizing the importance of social influences on health and disease. By targeting social and environmental factors, and interventions directed at changing interpersonal, organizational, community, and public policy, socio-ecological models have become pivotal in understanding the contribution of society, community, interpersonal and intrapersonal factors in disease prevention and health promotion. First noted by McLeroy and colleagues [250], the social-ecological framework (SEF) model, which is in fact a victim-blameless approach to disease according to Tesh and colleagues [251] resonates well with health policy measures associated with medical cannabis because it sets aside stigmatization. The implementation of public policy by a system-change approach alone, according to McLeroy and colleagues [250] is unlikely to succeed in a democratic and pluralistic society because it relies on the consent of the governed, failing to take into account the social causation of illness, and its departure from individuals and their choices. Socio-ecological models have proven useful over the decades

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[4] US Department of Justice. (2014). Drug Enforcement Administration, Office of Diversion Control. Controlled substance schedules. Retrieved from, https://www-deadiversion-usdoj-gov.proxy.library.nyu.edu/schedules/.

in assessing public health concerns as diverse as child abuse [252] and adolescent sports-related concussion [253].

Both quantitative and qualitative research methods have been employed in SEF models of marijuana use to guide public health policy. Berg and colleagues [254] studied correlates of level of marijuana use and driving under its influence among 649 subjects age 18 to 34 years, identified through Facebook ads targeting tobacco and marijuana users. The investigators [254] noted that more frequent use of marijuana and greater user friends led to enhanced motives and less concerns about driving under its influence (R-squared = 0.442). The authors [254] concluded that interventions and campaigns addressing social norms and risk perceptions of marijuana use would be successful.

Lamonica and colleagues [255] investigated the process of new policy implementation of medical cannabis in Massachusetts in 2012, when that state legalized medical marijuana under Chapter 369 of the Act of the Humanitarian Use of Medical Marijuana statute[5]. Analyzing qualitative data generated from ethnographic field notes, media reports, public records, and in-depth interviews with medical marijuana dispensary stakeholders, health care professionals, and patient consumers, and triangulated with a grounded theory approach, the investigators [255] noted gaps in transparency, communication, and education in the transition from illegal to legal status under the Massachusetts statute that governed the regulations for patients and caregivers, and permitted certification of physicians and the registration of marijuana dispensary entrepreneurs. Even after passage of the statute, and while public policy was being developed and implemented, the task of social re-construction of marijuana as medicine [256] was necessary, illustrating the social challenges associated with an illegal drug becoming a legal medicine. Social reconstruction theory, as described by Boeri and Lamonica [256] that proposes that most of which passes for knowledge in society is socially constructed, particularly common sense knowledge that constitutes the reality of everyday life for most of its ordinary citizens members [257], has reformed our concepts of marijuana use from early depictions of illicit

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[5] Retrieved from, https://malegislature.gov/Laws/SessionLaws/Acts/2012/Chapter369.

mindful behaviors [258] to a more modern view of the intricate interdependency of social, environmental, and individual biological determinants.

The experience in New York has not been formally studied. In 2016, the Commissioner of Health of the State of New York and the Department of Health certified its Medical Marijuana Program[6] delineated rules for registration and certification and prohibitions associated with health practitioners and facilities, and approved diagnoses that included specific severe debilitating or life-threatening cancer, HIV/AIDS, ALS, PD, MS, intractable spasticity, epilepsy, inflammatory bowel disease (IBD), neuropathies, Huntington disease (HD), cachexia or wasting syndrome, incapacitating pain, nausea, seizures, and muscle spasm. Additional regulations[7] passed in 2017, amending Section 502, Subpart 55-2 of Title 10 of the Public Health Law (PHL), allowed for the sale of medical marijuana products, provided for an improved experience for patients and visitors at dispensing facilities, and new courses for prospective practitioners to complete their training in a shorter amount of time were mandated, as well as making new forms of medical marijuana available and improving the dispensing facility experience. Under the new regulations, registered organizations were allowed to manufacture and distribute additional products including topical lotions, ointments and patches, as well as solid and semi-solid products including chewable and effervescent tablets and lozenges. Certain non-smokable forms of ground plant material were permissible for manufacture and distribution. All products were to be subject to rigorous testing and the DOH reserved the right to exclude inappropriate products or those which pose a threat to the public. In improving the dispensing facility experience, the new regulations allowed prospective patients and practitioners to speak directly with a registered organization representative, learn about products, and get information about the medical marijuana program. In addition, these measures will allow people other than designated caregivers to accompany certified patients to the dispensing

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[6] Retrieved from, https://www.health.ny.gov/regulations/medicalmarijuana/docs/regulations.pdf.

[7]   Retrieved   from,   https://www.health.ny.gov/regulations/medical_marijuana/docs/ 201712regulatoryamendments.pdf.

facility. In refining the training program for practitioners, the new regulations allowed for a shortened two-hour version of the present four-hour practitioner's course required to certify patients for medical marijuana. Other regulatory actions made a number of changes to help enhance the medical marijuana program including a broadening of the capability of ROs to advertise, streamlining the manufacturing requirements for medical marijuana products, amending security requirements, and clarifying laboratory testing methods, among other actions. Five ROs were authorized to manufacture and dispense medical marijuana in NYS to improve patient access, product pricing and availability and the geographic distribution of dispensing facilities across the state. As of August 2017, there were 26,561 certified patients and 1,155 registered health practitioners (HP) participating in the program. The number of certified patients increased by 11,569 (77%) since the addition of chronic pain in late March 2017.

A PILOT STUDY EXAMINING THE NEW YORK STATE MEDICAL MARIJUANA PROGRAM

In 2014, Governor Cuomo signed the Compassionate Care Act into law, establishing New York State's Medical Marijuana Program ("Program").[8] Three years later, during his Executive budget address, Governor Cuomo directed the DOH in consultation with other NYS agencies, to evaluate the experience, consequences and effects of legalized marijuana in neighboring states and territories, and to review the health, criminal justice and economic impacts of regulating recreational marijuana in New York. The DOH report [259] concluded that the positive effects of a regulated marijuana market in NYS outweighed the potential negative impacts. Areas that may be a cause for concern can be mitigated with regulation and proper use of public education tailored to address key populations. Incorporating proper metrics and indicators will ensure rigorous and ongoing evaluation. Inspired by the lack of perspectives from entrepreneurs, health care professionals,

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[8] https://www.health.ny.gov/regulations/medicalmarijuana/.

pharmacists, educators, and medical cannabis patients, this qualitative research study was performed to address gaps in the Program, and make further health policy recommendations using a SEF approach. Local stakeholders associated with Vireo Health, Inc., a certified New York State medical marijuana dispensary with locations in Queens, and White Plains, New York, were interviewed.

METHODS

After approval by the CUNY School of Public Health Human Research Protection Program to carry out this pilot study examining New York State's "Program," primary data was collected through the use of in-depth semi-structured interviews and demographic questions. The interview instrument employed was modified from an earlier study [255]. Each participant gave verbal consent to participate and each interview was not longer than one hour. A topic guide instrument was developed with major domains of stakeholders' personal views, community norms, attitudes, and behaviors, prescribing practices, knowledge of drug cost, insurance coverage, and financial subsidies, pharmacy and dispensing processes of medical marijuana ("cannabis"). Dedoose®, a cross-platform on-line application for analysis of qualitative and mixed methods research, was used for data analysis. Creating the codebook was a reiterative process. The process of making notes about themes immediately after completing each interview was followed by a review of contemporaneous notes which were grouped together as similar themes. Thence, an initial codebook was compiled from the coding of transcripts. After completing the first round of coding, another read through of the transcripts was performed to identify narrative sections that were not captured. A review of the data analysis outputs resulting from this initial coding was used to identify additional new codes and subthemes. The new codebook was entered into Dedoose and the transcripts were reviewed using the updated codebook and additional coding added to comply with the new codebook and definitions. As the sole researcher,

categorization and filtering of important themes and coding was an individual process.

Semi-Structured Interview

I am interviewing you today as part of City University's research study of New York State's Medical Marijuana Program. The purpose of today's interview is to learn about the experiences of various stakeholders involved and impacted by the process of legalization. By understanding the factors that may shape this process from the perspectives of various stakeholders, this study will highlight what is being done and provide recommendations for both policy and future research.

I want to start by asking you some questions, this interview is meant to be an informal conversation and you are encouraged to diverge into any areas that you feel are important to the topic. With your permission, I will be audio-recording this interview. This recording will be confidential. We will not include your name or any other identifying information on the transcript. Rest assured, the information, data, and reports that may come from this study, and our interview today, cannot be traced back to you. Your participation in this study is completely voluntary. You may refuse to answer any question or end the interview at any time without penalty. Therefore, if at any point you need me to turn off the recorder, please feel free to say so.

We ask people to choose a pseudonym, or a fake name, that we can use for your story. We include this name on the tape so your real name isn't attached to any of this information. What would you like your pseudonym to be? With your permission, I will start the audio-recording now.

INTERVIEWER: State the following information after you turn on the recorder:

1. Interviewer (your) name
2. Respondent's pseudonym
3. Date

Ice Breaker

First, I would like you to tell me a little bit about yourself without revealing specific information that would identify you. So, can you talk about yourself in terms of what you are doing at this time in your life, your goals, and any major experiences that impacted your life so far? Thank you for sharing this with me. Let's start talking about the topic of this study, medical marijuana.

Personal Views

1. Can you describe what you know about medical marijuana (MM) and medical marijuana legalization (MML)?
2. Can you speak a little bit about your views regarding MM before the MML bill passed? [Probe: indifference, concern, advocate, activist, experiences]
3. Can you describe any ways in which your views have changed since the bill passed?
4. Can you speak a little bit about your views regarding the recreational use of marijuana?
5. Can you describe your views on regular use of marijuana? [Probe: for yourself, your friends, and your family members]
6. Can you describe your views on the concept of marijuana as a "gateway drug"?
7. Can you speak a little about your views regarding medical marijuana dispensaries (MMDs) opening in this state? [Probe: diversion, dependence issues, crime]
8. Can you speak a little about how you feel about a MMD opening near where you live? Where you go to school or work?
9. What does the trend toward MML mean to you? [Probe: recreational marijuana, legal repercussions, health repercussions]
10. What does the trend toward legalizing marijuana mean to you? [Probe: other drugs, social repercussions, health repercussions]

Community Norms and Attitudes

11. Can you describe what you know about how MMLs affected states that passed MML bills already? [Probe: positive impact, negative impact; research; debates]

12. Can you describe what you know about the process for implementing MM here in New York? How did you learn this? [Probe: NYSDOH regulations; registration, public meetings]

13. Can you describe what you know about the process for opening a MMD here in New York? [Probe: NYSDOH regulations; registration, controversies]

14. What, if anything, have you heard about in your community (friends, parents, school) regarding a MMD opening? [Probe: In the community, nearby, bans, moratoriums, commercial boost; crime]

15. Can you describe for me the community where you live and the community where you go to school or work? [Probe: social and economic environment; political environment]

16. In your opinion, how will a MMD opening in or near where you live impact the community? Where you go to school or work? [Probe: no impact, negative, positive, not sure, Why?]

17. In your opinion, how do you think the members of the community where you live would feel about an MMD opening there? The community where you go to school or work?

18. Can you talk about who you see as the main people who will be impacted by MM in the community where you live? Where you go to school or work? [Probe: students, younger youth, drug users, homeless, criminals, commercial owners]

19. How will a MMD opening in the community where you live impact you? Where you go to school or work? [Probe: no impact, negative, positive, not sure, Why?]

20. Can you describe anything you have heard and your own opinions regarding dangers associated with a MMD? Of MM? Of marijuana?

21. Can you describe any side effects you know of or have heard of with the use of MM? Can you describe how these might be resolved?

Personal Norms and Attitudes and Behaviors

22. Can you speak a little bit about the health problems you think MM may be used to treat and why? [Probe: personal experiences, hearsay]
23. Can you describe what you know about the process of obtaining a medical marijuana registration card? About where MMDs will open?
24. Can you describe anything you have heard and your own opinions on MM causing a user to engage in more risky behaviors than typical?
25. Can you describe anything you have heard and your own opinions on recreational marijuana use causing a user to engage in more risky behaviors than typical? [Probe: sexual behaviors, multiple partners, drug injection behaviors]
26. Can you describe any impact you think MM will have on youth in this state? [Probe: interest, diversion, dependence, behaviors]
27. In your opinion, is there a need in terms of prevention services for young people who might have problems with marijuana use? If so, what is the most important need for addressing this?
28. Can you describe any health problems that you would like to use MM to treat?
29. Can you talk about any plans you have to get a MM registration card and why?
30. Can you talk about anyone you know who will be trying to obtain a MM registration card? If so, how do you know this person? What do you think of their reasons for needing a MM card?
31. Can you describe a time, if any, that you have obtained marijuana from someone who used it for medical purposes? If so, please describe how you obtained it. How did you feel about using MM illicitly? [Probe: fearful, paranoid, indifference, content, worth-it]
32. Do you think smoking marijuana regularly can be harmful? In what ways?

33. Can you describe how easy is would be for you to obtain marijuana right now if you wanted it?

34. What do you think your close friends think about using medical marijuana? About smoking marijuana for recreational purposes? About using it regularly?

35. If you plan to apply for a registration card, how do you think this will impact your life? Your future? Your parents? What are your concerns? [Probe: legality, diversion, dependence, cost]

Physician Specific Questions

36. Can you describe the process of prescribing MM to a patient?

37. Can you discuss how comfortable you are with prescribing MM to a patient?

38. Can you describe the process of being registered to prescribe MM?

39. How comfortable do you think most physicians you know would be with becoming registered? And with prescribing MM to a patient? Why?

Patient Specific Questions

40. Can you describe what you know about cost, insurance coverage, and financial subsidies for MM?

41. Can you discuss how comfortable you are with talking with your physician about MM?

Pharmacy Manager Specific Questions

42. Can you describe the process of being able to dispense MM?

43. Can you describe what you know of the cost structure, insurance coverage, or financial subsidies for MM?

Great! And now if we can just wrap up with a few standard demographic questions for context.

Demographics

1. What is your gender?
2. What is your age?
3. How would you describe your religion?
4. What kind of area were you raised in? Urban/rural/suburban/small town?
5. How would you describe your political orientation?
6. How would you describe your current employment status?
7. Can you estimate your household's combined annual incomes in thousands?
8. Where do you live? (Town/neighborhood)
9. What is the highest level of school you have completed or degree you have obtained?
10. How would you describe your ethnicity?

Thank you so much for sharing you experiences and making this pilot project possible.

Analysis

Demographics

The study cohort included 12 subjects from various locations both within the 5 boroughs of NYC and other areas in the state of New York. 7 of these were female, 4 were male, and one participant declined to specify. 4 of our participants were pharmacists, 4 were prescribing providers, 2 were patients, 1 was a patient care coordinator, and 1 was a Medical Marijuana Educator. We also gathered information regarding ethnicity, education, employment, age, and political identity in order to contextualize any trends that emerged in the data.

EMERGENT THEMES

Several different themes emerged overall and within three distinct areas of the implementation process for the application and registration process for opening dispensaries, the registration process for a referring provider, and the registration of qualifying patients.

Overall Themes

The codes that emerged most frequently overall were "Effective" and "Safe" as facilitators, and "Stigma" as a barrier. The code "Effective" was used when participants were speaking about the effectiveness of medical marijuana as a medication for various conditions and how this has been a facilitator for its legalization, acceptance, and use. The code "Safe" was used to identify areas where participants spoke about the demonstrated safety of marijuana as a medication which has shown to be much safer than other legal drugs, including being used to help patients come off opioids. It was also used to highlight areas where participants noted that legalized versions or the drug are even safer because they are regulated. The code "Stigma" was used to highlight areas when participants discussed misperceptions or personal stigmas as a barrier to legalization, acceptance, and use. It was also of interest to note that many of the participants that extolled the virtues, effectiveness, and safety of the drug, described that they personally would be uncomfortable asking for or becoming a medical marijuana patient.

Application and Registration Process for Opening Dispensaries

Themes in both barriers and facilitators to the process for opening dispensaries emerged from the interviews. Barriers to the process included "Process," which identified the very rigorous and competitive state process for applying, registering, and running a dispensary. The second theme that

arose was "Cost," which included the high amount of capital needed to apply, followed by the high overhead needed to continuously meet all the regulations, coupled with the relatively low revenue. These barriers have resulted in low numbers of dispensary companies and limited dispensary locations. They have also made the sustainability of the dispensaries as a business challenging.

There were also some themes that emerged as facilitators for the application and registration of dispensaries. One such facilitator was actually the regulations themselves. While the process and cost were seen as barriers to actually opening dispensaries, the various regulations regarding safety measures and dispensary rules of operation were seen as facilitators for community acceptance. The regulations that emerged as helpful ranged from the safety measures and video surveillance that may actually make the surrounding community safer, to regulations about products available which do not smell or lend themselves to people hanging around smoking. A second theme noted as a facilitator for opening dispensaries was job creation. A number of participants note that one of the benefits of the opening of dispensaries around NY would be the jobs that it created in those communities. Joe Dolce noted that this trend is being seen nationwide, with the number of people working in the cannabis field already surpassing other more ubiquitous fields, such as bakers.

Registration Process for a Referring Provider

Once again the intensive process was noted as a barrier. This barrier includes the process of becoming a referring provider and the extra hoops that providers have to go through after they are registered in order to create a referral for each patient. This process generally included gaining approval from the place you are employed, taking the class, passing the test, sending paperwork to the state, getting registered, learning the recommendation system, opening a website or telling patients about the options, and then going through the prescribing process with each patient each time. A second barrier was the education regarding medical marijuana for providers.

Becoming registered requires a 2 hour course be taken, this is reduced from the 4 hour course that used to be required. While the reduction in hours does reduce the time investment needed for a provider to become registered, it was mentioned by many that it was completely insufficient. It was also noted that the education on cannabis in Medical School and the available resources and studies online are also lacking. There were a few strong themes that emerged as facilitators for registration of providers. The research coming out and the personal experiences of patients showing medical marijuana's use for treating a number of complaints and conditions more effectively that the current standard of care was highlighted as a facilitator for getting more providers interested in going through the registration process and being willing to go through the extra hoops necessary to recommend patients for this treatment. Another motivating factor for providers is the safety profile of medical marijuana. Many of our participants noted the minimal side effects compared to current standard drugs. They also highlighted the opioid epidemic and the potential to save lives with a painkiller with a higher safety profile. While neither of these facilitators helped facilitate the actual process, they were seen to facilitate the number of providers becoming registered by increasing motivation and interest.

Registration of Qualifying Patients

This study also examined barriers associated with the registration of qualifying patients. A major barrier noted by all the stakeholders was the process from the patient side, such as finding a registered provider, bringing documentation of their qualifying condition, having a NY resident ID, registering on the state website, waiting for the card, having a consultation with a pharmacist. It is quite a bit more effort than patients have to put in for other medications. Another major barrier is cost. As a federally illegal substance, insurance companies do not currently cover the cost of the medication, putting the medication out of reach for a large number of patients that could potentially benefit. Another barrier that emerged was stigma. Patients may themselves carry stigma towards the drug or may be

concerned that others will judge them for using the medication. Even among our participants who spoke strongly against the stigma surrounding medical marijuana, they noted that they would be hesitant themselves to register for a card. Some listed the reason as wanting to promote legitimacy, some indicated that the fact that it was still federally illegal or that they didn't know if their medical boards would like it made them hesitant, and a few seemed to realize during the interview that they were in their own words "hypocrites" regarding the stigma. The study also highlighted some facilitators associated with the registration of qualifying patients. One of the facilitators for registration of patients that came up frequently was legalization itself. The very act of legalizing means that patients are more likely to consider medical marijuana as a medication. Another big facilitator for patients becoming registered is education, both the growing understanding of how effective this medication can be and education about the process for registering. This can be from personal experience, shared stories of other patients, reports coming out, providers talking about it, but the more patients hear and learn about the possibilities, and the more they are educated on the process, the more interested and able they are to navigate the program.

Code Co-Occurrence

The co-occurrence of themes also highlighted important interactions, for example, co-occurrence was highest for the codes "Safe x Effective." Both of these were seen as facilitators for the program, the fact that there is now an option for a relatively effective medication for a variety of conditions that has a much higher safety profile than many standard of care medications is a strong support for the program. The next most frequently co-occurring themes were "Limited Qualifying Conditions" as a barrier to the program and "Effectiveness" of the medication for many conditions as a facilitator. This tension highlights the theme that arose in our interviews that New York is being slow to expand the uses of medical marijuana, which may be doing a severe disservice to patients that could potentially benefit. "Stigma" as a

barrier for use frequently co-occurred with "Education" as a need or as a facilitator for the program, suggesting that education is the best way to combat stigma and support the program.

"Federal Legalization" was a barrier frequently co-occurred with "Cost" as a barrier, which highlights the problematic aspects of making medical marijuana legal, and therefore available, in the state of New York, while failing to make it actually accessible to many patients who could benefit from it.

DISCUSSION

The themes that emerged from the interviews highlight tensions in the Program. While tightly regulating the process of certification for all stakeholders (physicians, patients and dispensaries) may be seen as a benefit in regards to providing physician education, assuring the appropriateness of cannabis products for patients, and mandating dispensary safety measures, pharmacy consultations, and quality regulation of medications; the bureaucratic slowness of the process and extra steps were regarded as barriers. These barriers highlight New York State as being behind the science and actively depriving patients of potentially beneficial medication. These often mentioned barriers included the onerous registration process for providers and patients, overly lengthy (10,000 page) application for the dispensaries, and limits placed by New York State on the number of dispensaries and approved diagnoses.

Although New York State's Program suggest an otherwise simple straightforward process toward patient receipt of medical cannabis (Figure 6), stakeholders that were interviewed suggested otherwise.

> *Yes, you have to go and do the classes and pass the test, and then send your paperwork to the state and wait for the approval by the state, and then get registered, and then they'll figure the health commerce system. And then start prescribing and open up a website, or tell your patients what's going on and convince them that they need it and it's available to them,*

and it will work. And it's better than everything else. So there's a lot of hurdles there. Lots and lots and lots of hurdles (Daley, Physician).

So, it took me until the end of last year to go through the hoops at my work and get them to give me the okay to get certified and be able to prescribe for our patients. I do feel like my education in marijuana itself is pretty sorely lacking, and even the required course that I took was pretty minimal in terms of the amount of information that was available to me, the amount of information that it was required for me to have in order to prescribe. Even the sources out there for additional information, just prescribing wise whether it's a side effect profile, or what populations would benefit most from it, I still have kind of yet to really feel like I have a good amount of knowledge on the subject. (Anne, Physician).

Pertinent views of the limitation of access to medical cannabis in New York State were voiced by other interviewees, including its use in a restricted number of medical condition, divulging professional information to government offices, high cost, lack of available insurance coverage, notwithstanding its safety compared to opioids or the medications that are presently used to combat addiction:

I know that it is effective with certain conditions. I know that there are many conditions out there that it is not approved for. And I have seen some really remarkable results with the use of medical marijuana for sick patients (Lydia, Physician).

So why do they need to create an account with the Health Commerce System at all? Why can't we do that as prescribers since we're doing that for basically everything else? I can order chemotherapy for somebody and they don't have to do a thing, but for medical marijuana they do. There's a huge step that involves patients, which for every other drug they don't have to do that. So I would take away that involvement, because I feel like that's really limiting people's ability to get the medication they need. (Anne, Physician).

Doctors have a new option for pain management and I think that the way that our minds are changing about opioids, this is going to be a much more useful option and a much more not only useful option but, for one it's a safer option. You know we should have fewer opioid deaths (JC, Pharmacist).

It's difficult because I'm on disability. So, I only have a limited amount of income. It's hard when you have to choose between medication and another necessity of the house because insurance doesn't cover medicinal marijuana. So, I don't understand how the government would love to pay

for opioids to keep me as a zombie, but not my cannabis that makes me productive. I can't grasp that idea. (Starr, Patient).

Figure 6. The four step process of medical cannabis purchase that begins with contacting a certified provider and visiting an approved medical cannabis dispensary. Reprinted from, https://www.health.ny.gov/regulations/medical_marijuana/patients/.

> *I think, once again, it's a negative opinion about it. "Oh, you have cannabis, you're using medical marijuana." It's like, "Oh, we want to avoid it." And that's how I think the whole medical community is in general. We don't have enough providers giving it. We have more providers giving Suboxone and the Buprenorphine, and writing opiates than we do have cannabis. And that shows you right there. In fact, it should be the opposite way. Cannabis should be first and opiates should be last. But nope, it's the opposite, so ... We're all stuck with it.*

RECOMMENDATIONS

Viewed through the lens of a public health SEF and the real-time perspectives from dispensary entrepreneurs, health care professionals, and patients, it is possible to clarify the actors and social and environmental factors, and gaps in health policy relevant to the success of New York State's medical marijuana program. The SEF model places society and health policy at the highest level, notably stakeholders in policy development, dissemination, enforcement, evaluation and revision; followed by community factors below, and interpersonal relationships and intrapersonal factors below. At the societal level, decriminalization remains the greatest obstacle to destigmatizing medical cannabis. Legalization at the national

level should be continued because it has the potential to reduce barriers posed by high cost and lack of insurance coverage. There is a need for an expansion of qualifying conditions for medical cannabis, and expansion in the number of dispensaries. At the community level of physicians, pharmacists, and entrepreneurs there needs to be not only effective education and destigmatization of medical cannabis, but also supportive networks for sharing information, consistency in prescribing, and the development of evidence-based algorithms adjusted to diverse patient populations and applicable products. At the intrapersonal and interpersonal level, qualitative ethnographic studies incorporating the views of individuals have the potential to provide valuable insights into the lives of patients and their friends, caregivers and family members. Education on the uses and effects of medical cannabis marijuana, and the location of dispensaries and their regulations need to be available and easily accessible. It is further important for stakeholders to be racially and historically sensitive to the possible stigmatizing aspects of marijuana so as not to create barriers to its medical use.

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For the past three decades, the author, David S. Younger MD, MPH, MS has been a clinician, educator, and more recently, public health researcher and advocate. Dr. Younger is an authority in the use of immunotherapy to treat childhood and adult neuro-immunologically-mediated disorders. He has edited or authored several books, including *Motor Disorders 3rd Edition, The Vasculitides*, *Human Lyme Neuroborreliosis*, and *Global and Domestic Public Health and Neuroepidemiology*; and is writing the popular book, *The Autoimmune Brain*; and *Neuroepidemiology: The Basics and Beyond*. He has authored more than 250 peer-reviewed articles, book chapters, and abstracts. He has been a member in the Department of Neurology, Division of Neuroepidemiology of New York University School of Medicine, and is a current doctoral trainee in the School of Public Health, Department of Health Policy and Management at City University of New York.

Dr. Younger obtained his MD degree from Columbia College of Physicians and Surgeons in 1981, afterward entering internship and

residency in Internal Medicine at Montefiore Hospital, and completing while returning to Columbia University Neurological Institute to start his first year in residency, straddling the two worlds. He continued his training in three postdoctoral fellowships: epilepsy and electroencephalopathy, clinical neuromuscular disease and electrodiagnosis; and clinical trials at the Neurological Institute where he was mentored by "Bud" Rowland, Chairman of the Department of Neurology, and Editor-in-Chief of the journal *Neurology*. Dr. Younger remained at Columbia University as an Assistant Professor of Neurology until he moved to New York University becoming Clinical Associate Professor, and the first Chief of Neuromuscular Disease.

Frustrated by the lack of connection with larger populations and understanding disease risks and public health policy reform, he entered New York University College of Global Public Health master's degree program in public health, followed by a master's degree program in epidemiology at Columbia Mailman School of Public Health. Urged by colleagues and family to obtain further leadership and research training in public health, Dr. Younger then embarked on a doctoral degree program in Health Policy and Management at City University of New York School of Public Health in the fall of 2017, where he anticipates graduating in 2020. He hopes to use this final degree to promote health policy reform for larger populations than his own clinical sphere.

It was during the doctoral program of the past year that his interest medical marijuana piqued, as he recognized the immense scientific and public health aspects of the drug citing four reasons for pursuing the present book. First, curiosity in the medical scientific aspects of the endocannabinoid system in the brain and immune system. Second, the effectiveness of medical marijuana in promoting healing and alleviating the suffering of many patients. Third, public health aspects associated with the legalization of marijuana and dispensing it in the many formulations of medical cannabis. Lastly, the paucity of public health policy research

evaluating the experience of stakeholders, cost effectiveness and benefit analyses associated with medical cannabis compared to other treatments.

His website: http://www.davidsyounger.com, provides a useful toolbox of on-line resources.

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Cannabis: Medical Aspects

Editors: Blair Henry, Arnav Agarwal, Edward Chow, Hatim A. Omar, and Joav Merrick (Sunnybrook Health Sciences Centre, Toronto, ON, Canada, and others)

Series: Health and Human Development

Book Description: The typical recommendation for physicians is that medical cannabis should not be a first line therapy and that documentation should outline that conventional therapies were attempted, but were not successful. In this book, we look at the many aspects involved with the medical use of cannabis.

Hardcover ISBN: 978-1-53610-510-0
Retail Price: $160

Medical Cannabis: Clinical Practice
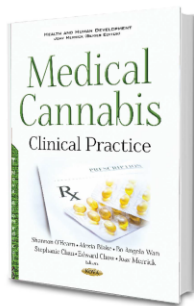
Editors: Shannon O'Hearn, Alexia Blake, Bo Angela Wan, Stephanie Chan, Edward Chow and Joav Merrick, M.D. (MedReleaf, Markham, Ontario, Canada, and others)

Series: Health and Human Development

Book Description: Medical cannabis is emerging as an effective treatment option for the management of a variety of common chronic conditions and symptoms, but a lack of scientific evidence demonstrating its efficacy for treating specific indications is hindering the widespread clinical adoption of medical cannabis.

Softcover ISBN: 978-1-53611-907-7
Retail Price: $82

## Cannabis Sativa for Health and Hemp

Editor: Ethan L. Clark
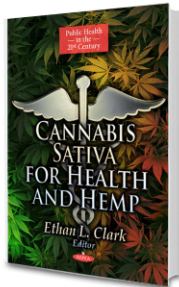
Series: Public Health in the 21st Century

Book Description: The issue before Congress is whether to continue the federal prosecution of medical marijuana patients and their providers, in accordance with the federal Controlled Substances Act (CSA), or whether to relax federal marijuana prohibition enough to permit the medicinal use of botanical cannabis products when recommended by a physician, especially where permitted under state law.

Hardcover ISBN: 978-1-61209-982-8
Retail Price: $162

Medical Marijuana and Marijuana Use

**Editor:** Zossima Pirogov
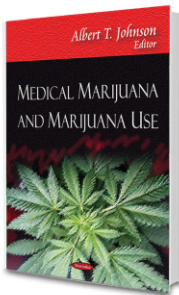
Book Description: Twelve states, mostly in the West, have enacted laws allowing the use of marijuana for medical purposes, and many thousands of patients are seeking relief from a variety of serious illnesses by smoking marijuana or using other herbal cannabis preparations. Meanwhile, the federal Drug Enforcement Administration refuses to recognize these state laws and continues to investigate and arrest, under federal statute, medical marijuana providers and users in those states and elsewhere.

Softcover ISBN: 978-1-60692-899-8
Retail Price: $59

Marijuana: Medical Uses, Regulations and Legal Issues

EDITOR: Margie Vasquez
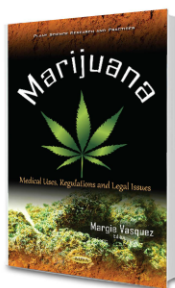
SERIES: Plant Science Research and Practices

BOOK DESCRIPTION: Cannabis sativa is the scientific name for the widely used drug commonly known as marijuana. Marijuana is the most commonly used illegal drug in the United States as well as in many other countries. Considered a "soft" drug, it is a naturally growing plant that is harvested as its crude product for use.
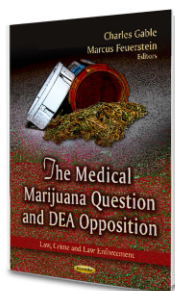
HARDCOVER ISBN: 978-1-63484-409-3
RETAIL PRICE: $110

The Medical Marijuana Question and DEA Opposition

EDITORS: Charles Gable and Marcus Feuerstein

SERIES: Law, Crime and Law Enforcement

BOOK DESCRIPTION: This book will review the federal government's constitutional authority to enact the federal criminal prohibition on marijuana; highlight certain principles of federalism that prevent the federal government from mandating that states participate in enforcing the federal prohibition; consider unresolved questions relating to the extent to which state authorization and regulation of medical marijuana are preempted by federal law; and assess what obligations, if any, the U.S. Department of Justice (DOJ) has to investigate and prosecute violations of the federal prohibition on marijuana.

SOFTCOVER ISBN: 978-1-62417-080-5
RETAIL PRICE: $69