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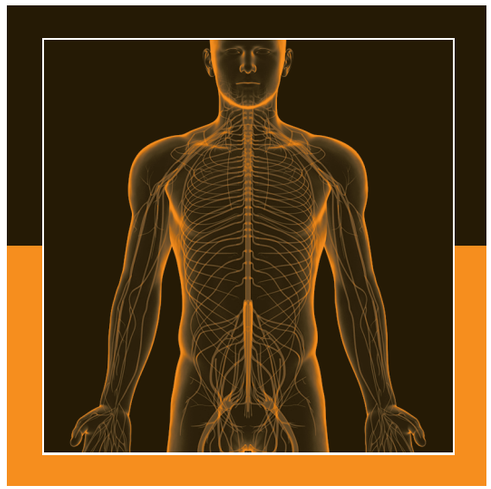

Cannabis: The Never-ending, Nefarious Nepenthe of the 21st Century: What Should the Clinician Know?

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Foreword

With the recent spate of state-based legislations authorizing medical cannabis use along with recreational cannabis use, physicians have been placed in the position of advising patients as to its use. With multiple agencies usually involved in the cannabis industry (e.g., Department of Public Health, Department of Agriculture, Drug Enforcement Agency, and Department of Financial and Professional Regulation among others), guidance and information for the primary care practitioner may be conflicting and difficult to obtain. This can be especially true in issues of cannabis and its adverse effects since the pharmacology of cannabis can be quite complex. Thus, cannabis-related medical issues and impairment may be somewhat challenging to predict and identify from the perspective of the primary care physician. This issue of Disease-a-Month by Dr. Donald E. Greydanus and his colleagues provide guidance on these very difficult clinic issues.

Jerrold B. Leikin, MD
Editor-in-Chief

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Introduction

Cannabis (marijuana or pot) remains a controversial plant in the 21st century. This discussion considers a number of issues regarding cannabis including a historical perspective, description of the *Cannabis sativa/indica* plant, means of consumption, prevalence of use, links to polydrug use, cannabis lab testing, and cannabis pharmacology (Table 1). Also considered are the many potential adverse medical and psychiatric effects found with smoking cannabis. The issue of "medical marijuana" is then presented, which is a hotly discussed topic in national- and state-level politics, the criminal justice system, and now in medicine across the board. As such, there are entanglements in the discussion of marijuana as medicine that need to be dissected out in order to clearly examine its potential medicinal legitimacy. This article reviews concerns regarding smoked marijuana, physician liability issues, and The American Society of Addiction Medicine's recommendations regarding medical marijuana.

The information provided will help physicians assess a situation in which the risk–benefit ratio to the patient *and* the doctor as well should be carefully weighed. Finally, it reviews what primary care clinicians can do in identifying and facilitating treatment for an increasing number of persons who develop cannabis-related disorders. This discussion reviews the main characteristics of a robust program termed Screening, Brief Intervention, and Referral to Treatment (SBIRT) and offers a "how to" basic implementation guide for the primary care office. Other available behavioral and pharmacological options are also reviewed to familiarize clinicians with the type of care patients receive when the severity of the condition requires referral to specialists.

Historical perspectives

A number of euphoric and hallucinogenic plants have been utilized by human beings for the thousands of years of recorded history and presumably long before the cuneiform writing

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Table 1
Outline of the publication.

Historical perspectives
Cannabis sativa/indica plant
Means of consumption
Cannabis prevalence
Links to polydrug use
Cannabis lab testing
Cannabis pharmacology
Adverse medical effects of cannabis consumption
Other adverse cannabis effects (i.e., pregnancy, poisoning, and MVAs)
Adverse psychiatric effects of cannabis consumption
Medical marijuana
Recommendations of the American Society of Addiction Medicine (ASAM)
Primary care office response: SBIRT program
Behavioral management of cannabis-related disorders
Pharmacologic management of cannabis-related disorders
Conclusions

system was initiated by the ancient Sumerians of Mesopotamia in 3200 BC. These plants include *Cannabis sativa/indica*, *Papaver somniferum, Rivea corymbosa, Datura stramonium, Datura candida, Pancratium trianthum, Atropa belladonna, Erythroxylum coca, Hyoscyamus niger, and others*. Use of *Cannabis sativa*, the hemp plant, to make fabrics dates back to 8000 BC, while hemp seeds used as food has been traced to ancient China in 6000 BC.[1]

Cannabis has remained an accepted plant for medicinal, religious, and/or euphoric properties from ancient Asia (i.e., China, India, and Tibet) to modern times.[2,3] *Cannabis sativa* is one of the oldest plants cultivated by humans, and controversial claims of euphoria-induced treatment of complex illnesses (i.e., chronic pain, seizures, spasticity, nausea, and others) date back many millennia to the dawn of recorded time.[4,5] It has remained a popular plant since antiquity, earning many colorful and descriptive sobriquets or noms de guerre such as pot, weed, grass, tweed, hash, hemp, afternoon delight, puff puff pass, left-handed cigarette, Puff the Magic Dragon, and a sesquipedalian number of others coined by its dedicated smokers.

The father of Chinese medicine Emperor Shen Nung (2737 BC) compiled a classic classification of medicines—Pen Ts'ao; in this work, he included cannabis.[6,7] The Hindu sacred text Atharva Veda lists cannabis as one of its five sacred plants calling it "sacred grass" ; cannabis was used in India as medication as early as 1200 BC.[1] *C. indica* has been used for thousands of years in India to worship god Shiva; it is used on special days in pills (bhang) prepared from wet resinous leaves or in a milk-prepared form with various spices added. Special males who live as holy persons can smoke the cannabis flowering buds as part of their worship practices. The Hindu use of cannabis involved low doses (thandai and chilam), specific times of use (i.e., evening), and for specific purposes (i.e., to enhance ritualistic ceremonies); high doses of cannabis (i.e., ganja and charas) were avoided and considered as poisons.[8]

The Greek historian Herodotus (490 BC–425 BC) wrote in 430 BC that the Scythians (war-like Iranian equestrian tribes of the 8th to the 3rd centuries BC) used cannabis to make clothes, in funeral rituals, and to purify themselves in baths with cannabis smoke.[9,10] The famous Chinese philosopher Confucius (551 BC–479 BC) commented on cannabis as a product to cultivate and consume.

Cannabis was not written about in ancient Greece and seems to be known only to the ancient Chinese and Hindus.[11] In the classic, ancient Greek epic poem Odyssey by the Greek poet Homer (8th century BC), there are fascinating clues to a fabled chemical called "nepenthe" that was used to allow disappearance of sadness and rage from one's memory presumably via the development of drug-induced euphoria.[10] It is known that wine (not cannabis) was used in ancient Greece both to make persons happy and a way to take other drugs; wine was mixed with other ingredients to make "kyphi" in ancient Egypt.[10] Mythology has identified cannabis as being one of the ingredients in the Old Testament mention of holy anointing oil (Exodus 30:22–23—1400 BC), though this remains controversial among scholars.

One of the famous Greek physicians to the Romans as well as an acclaimed botanist Dioscorides wrote his classic medical test *Materia Medica*, which referred to cannabis in 70 AD as a material to both make strong rope from the Cannabis stalk and treat ear pain and low libido.[1,12] Galen (129 AD–200 AD), an even more famous Greek physician to the Romans, wrote about a pot-seed desert consumed by Romans that could cause overdose symptoms.[1] Hashish was well known in the Middle East from the 9th century and beyond.[13]

The 16th century Chinese medical textbook writer Li Shi Chen (1517–1593) discussed the use of cannabis as medicine.[1] The French and British grew cannabis in early America in Virginia and Plymouth in 1632, and this plant remained accepted in the 17th, 18th, and 19th centuries in the West.[14–16] It was more established in Europe (i.e., Paris, London) at the end of the 18th century after the Egyptian campaigns (1798–1801) of Napoleon Bonaparte.[10] The Americans became particularly involved with cannabis use in the 19th century, with leading artists such as the Latin-American poet Porfirio Barba-Jacob (1883–1942) and others being influenced by heavy use of cannabis.[17]

Cannabis remained an accepted plant from its earliest beginnings until the 20th century. In the early 20th century, cannabis was accepted along with the availability of aspirin and opioids.[7] However, concern about cannabis arose in the early part of the 20th century. For example, during the 1925 League of Nations' Second Opium Conference, authorities from Egypt provided an alert to the dangers of cannabis, as they argued that Indian hemp was as dangerous as opium and should be subjected to the same international controls as opium; this was accepted by a number of other countries, though neither England nor its then colonial powers agreed with this conclusion.[18] Physicians in 19th and early 20th centuries in America recommended cannabis for a variety of medical problems.[19]

Concerns about cannabis arose in the US federal government even as the prohibition of alcohol that was started in 1920 was then removed in 1933. One of the concerns was about the perceived problems related to getting different doses of cannabis with various purities.[3] Issues over the purity and potency of different cannabis products have been debated in many cultures over the centuries.[20] Despite the advice of the American Medical Association to the contrary, the US government criminalized cannabis with the passage of the 1937 Marijuana Tax Stamp Act, making it illegal to buy, sell, barter, or give marijuana away in the US.[7,21]

Vietnam War decade

The 20th century also witnessed the scientific study of this plant that has slowly revealed some of its properties that were secret for millions of years. Plant cannabinoids were identified in the 1960s, and the euphoric ability of this plant was traced in the mid-1960s to the psychoactive chemical delta-9-tetrahydrocannabinol (THC).[1,22,23] THC was identified in 1964 by Professor Raphael Mechoulam, an Israeli organic chemist.[24–26] The identification of THC in cannabis also occurred at the turbulent time in America partly due to the controversy regarding the Vietnam War (1965–1975) with its era of war protests, hippies, and social pro-cannabis attitudes including cannabis use by the American military in Vietnam.[27,28]

This "Vietnam War decade" set the stage for the current controversies in cannabis in this second decade of the 21st century. As evident today, elements of the American society in this Vietnam War decade who had fame and power and who found cannabis consumption a positive experience advocated for its legalization as well as widespread availability.[29,30] The identification of THC helped to clarify the underpinnings for addiction or dependence that has long been seen in some cannabis consumers by clinicians as well as scientists.[31–34] During this era, a number of authors listed possible concerns with adverse effects of cannabis in articles published in the medical literature.[35–40] A report was given to the government, and concern with pot use by adolescents was raised.[41,42]

Interest at all levels of society was now stimulated, which continues to the present time. Other indications of the US Government concern can be found in the Federal, Food, Drug, and Cosmetic Act of 1962 and the Controlled Substances Act of 1970.[43] In 1968, the US Congress

mandated that studies be done to look at effects of long-term use of cannabis in humans, and regular reporting took placed in the early 1970s, looking at what was called "Marijuana and Health."[43]

Marijuana was classified by the US Congress as a Schedule I substance in 1970, stating it was illegal and without medical value.[19] Anecdotal reports were seen suggesting that cannabis was beneficial for medical issues such as severe nausea and emesis from cancer chemotherapy as well as reduction of high intraocular pressure in glaucoma.[43] Efforts were increased to legalize cannabis—efforts that have been intensified in recent years. California was the first state to legalize the medical use of marijuana in 1996.[19]

Despite the refusal of the government to legalize pot and the tentative concern of various scientists, cannabis continued to be consumed by countless millions of human beings. Parents who consumed pot in the 1960s and 1970s had a hard time telling their adolescents in the 1980s and 1990s to avoid it.[44] Cannabis continued to grow in popularity, and curiosity about this plant was stimulated when endogenous cannabinoids, cannabinoid receptors, and the cannabis endocannabinoid system in the central nervous system were identified in the 1980s and 1990s based on research on cannabinoid pharmacology that began in the 1940s.[3,22,45–47] Research into the mechanisms of cannabinoids and endocannabinoids has stimulated the current search for potential medicinal uses of parts of the cannabis plant.[48] In addition, the end of the 20th century saw a global resurgence in the acceptance of the euphoria found with cannabis.[10]

Au courant society

Today, cannabis remains the most common illegal drug consumed, and euphoric cannabis consumers are mounting enormous pressure to legalize this plant to a wide audience, as has been recently witnessed in the states of Colorado as well as Washington and partially fueled by the perceived failure of alcohol prohibition that ended in 1933.[48–50] As the tide turns again toward open and global acceptance of this complex euphoric plant, the free market including the tobacco organization and/or various food/libation groups are preparing to enter this potentially lucrative field with enormous effects on billions of humans in this century.[51–53]

In such a milieu, this article takes a look at what we know about this controversial plant of antiquity and what clinicians should tell their patients in an age where fame and fortune advocate for its current release to society much as alcohol was released 7 decades ago in the United States. Cannabis ("*puff the magic dragon*") has survived various efforts to stop its use, and it is a popular, beloved drug in the 21st century.

Cannabis sativa/indica plant

Cannabis is a genus of a flower plant grown all over the world but indigenous to Central and South Asia; it has three species: *C. sativa*, *C. indica*, and *C. ruderalis* that belong to the family Cannabaceae (Table 2). The *Cannabis indica* plant is a shorter plant than *C. sativa*, with broader leaves, which has also been used down through the ages.[13,16,54,55] It is the same plant and found throughout cannabis plants in the United States with widespread introduction in the 1970s.[56]

Table 2
Cannabis classification.

Family: Cannabaceae
Genus: Cannabis
Species:
C. sativa
C. indica
C. ruderalis
Psychoactive chemical: *delta-9-tetrahydrocannabinol* (THC)

C. ruderalis was originally from Central Russia, is found in the United States, and is typically not grown by recreational users because of its relatively low *delta-9-tetrahydrocannabinol* (THC) content (*see below*).

C. sativa and *C. indica* are dioecious annual herbs (angiosperm) that are relatively easily grown, and their euphoric properties are linked to cannabinoids in the plant, with much of the research focusing on *delta-9-tetrahydrocannabinol* (THC). The product that is sold as cannabis is processed from the plant's dried leaves, seeds, stems, flowers (sensimilla), and oil.[56,57] Depending on the strength of THC, a psychoactive state or euphoria develops, lasting minutes to hours, and that induces such reliable *relaxation* that irresistibly brings the user back for more euphoric tranquility.[58] The state of relaxation may be more pronounced with cannabis made from the *C. indica* plant.[56] This euphoria is also characterized by a change in one's perception of time and the importance of the present as it relates to the future.[8]

THC pharmacodynamics involve the action of the enzyme, Δ1-tetrahydrocannabinolic acid synthase, which catalyzes oxidative cyclization of cannabigerolic acid (CBGA) into the precursor of THC—Δ1-tetrahydrocannabinolic (*see below*).[59] The psychoactivity of this plant is controlled by this enzyme, and the potency of cannabis has varied over time. THC in the cannabis of the 1960s–1970s was usually 1–2%, while THC in the Hawaiian sensimilla product was 3%. THC potency in the late 1980s was as high as 7.8%.[20] Higher levels have been noted by the Potency Monitoring Project and others, while a recent Japanese survey found an average potency of 11.2% but a high of 22.6%.[20,60,61]

Consumption of cannabis (marijuana)

Marijuana can be consumed orally in various foods (i.e., cookies, brownies, spaghetti, and others), teas, or capsules (Table 3). Numerous food products are prepared in different countries, as for example, a "pie" called *Majoon Birjandi* is eaten by some youth in eastern Iran as a way to experience euphoria.[62] As noted by Galen in 2nd century Rome, clinicians today should warn these consumers that one could become ill from eating too much pot pie.[57]

The typical and most favorite method of using marijuana is to smoke it as a joint in which the marijuana (bhang) cigarette is rolled from the *C. sativa/indica* plant using plant parts (i.e., leaves, stems, and tops) that are cut and dried (Table 3). Hashish (Hash) is made from dried exudates coming from the plant's top and underside of its leaves, while hashish oil refers to concentrated hashish distillate. Another potent pot product is made from the seedless female flower of *C. sativa* and is called sensimilla. In a study published in 2009 in France, of 90 cannabis users seen in an outpatient setting for cannabis use disorders with an average age of 27.5 years, the main way to take this plant was to smoke a blunt; 75% consumed cannabis in the form of hashish (resin) and one-quarter as marihuana (grass).[63]

As cannabis becomes legalized in more and more states, manufacturers will be advertising about having the "best" methods in this process to make the "perfect" joint much as cigarette or alcohol producers have done in the 20th and 21st centuries for their lucrative products. Today, the commonly available cannabis cigarette contains approximately 20 mg of THC produced from

Table 3
Modi operandi of cannabis consumption (see text).

Oral: cookies, brownies, spaghetti, others
Smoke plant parts: leaves, stems, tops
Smoke hashish
Smoke hashish oil
Smoke sensimilla
"Boosting": add marijuana to tobacco or other drugs
Hookah pipe
"Dabbing" (uses butane hash oil)
Hotboxing (cannabis smoking in a closed car with peers)

a gram of the plant's leaves and buds. In the previously noted French study of 90 adults with cannabis use disorder, cannabis consumption during the last 6 months was about 5.8 blunts per day and 12 g per week.[63]

Depending on the production process, considerable variability is found in the potency of the pot cigarette,[64] though THC is usually detectable in the consumer for up to 2 weeks after smoking one joint. The effects not only vary with the THC potency but also with the addition of other chemicals cannabis consumers may use. For example, a blunt is a cigarette or cigar made from tobacco with variable amounts of marijuana added in a classic production process called boosting; as discussed later, cannabis is also smoked along with other drugs (i.e., alcohol) to boost the effects of the euphoria (*see below*).[65] Smoking cannabis using a hookah pipe is a popular method with many adolescents, college students, and even health sciences students.[66]

New methods of consumption are always sought out by the afficionados of these products, as noted with the e-cigarette development in tobacco (Table 3).[67,68] In the pot consumption world, a new way of partaking cannabinoids is emerging that is called "dabbing," which uses butane hash oil in contrast to smoking flower cannabis and may lead to the potential risk of increased cannabis dependence.[69]

Prevalence

Precise prevalence data for cannabis can be problematic to obtain, though information from various sources conclude that this plant remains the most popular illicit drug in the world (Table 4).[1,70–72] As its status of illegality changes to being a legal drug from place to place, pot use will only increase. Some researchers suggest that it is not the amount of cannabis use that is the issue, but the amount of use that results in harm to the person.[73]

Methods to identify population pot prevalence include wastewater (sewage) studies, cigarette paper sales, and the classic self-report data.[74–76] Reliance on opinions of drug consumers for how much of a drug is consumed is not reliable, since research suggests that one who takes a drug may have an inaccurate estimate of how much others are using, and this is influenced by the person's consumption; those who overestimate the use of others tend to overuse the drug themselves.[77]

The European School Survey Project on Alcohol and Other Drugs (ESPAD) studies alcohol and other drug consumption by 16 year olds in Europe. The ESPAD was started in 1995, and there is a repeat survey every 4 years. The 2011 ESPAD study published data on 100,000 adolescents in 36 European countries and noted an average lifetime cannabis use of 17% with a range of 4–42%; the 2007 ESPAD had an average of 19% with a range of 4–42%.[78] One-third of Canadian university students use cannabis.[79]

The top three drugs consumed by adolescents in the United States are tobacco, alcohol, and cannabis, while the latter, though currently an illicit schedule I drug in most places in today's

Table 4
Cannabis prevalence (see text).

2007 AD[a]: lifetime cannabis use of 19% (range of 4–42%)[78]
2013 YRBSS[81b]:
(a) Lifetime cannabis use: 40.7% (31.3% in 1991)
(b) Current use: 23.4% (14.7% in 1991)
(c) 8.6% Of youth under the age of 13 years had experience with cannabis
2013 US NSDUH[82c]
(a) 24.6 Million Americans aged 12 years or older used illicit drugs
(b) 19.8 Million past-month users (7.5% of those 12 years or older)

[a] European School Survey Project on Alcohol and Other Drugs (ESPAD).
[b] Centers for Disease Control Youth Risk Behavior Surveillance Survey (YRBSS).
[c] National Survey on Drug Use and Health (NSDUH).

America, constitutes 75% of the illegal drug trade in America.[1,57] The United States Centers for Disease Control and Prevention (CDC, Atlanta, GA) reported a lifetime use (once or more times) of 31.3% of American high school students in 1991 in its YRBSS (Youth Risk Behavioral Surveillance System); this rose to 47.2% in 1999 and then was 36.8% in 2009.[80]

The 2013 YRBSS included a national school-based survey conducted by CDC, 42 state surveys, five territorial surveys, two tribal government surveys, and 21 local surveys conducted among students in grades 9–12 during October 2012 to February 2014.The CDC reported a lifetime cannabis use of 40.7% (versus 31.3% in 1991) and a current use of 23.4% (versus 14.7% in 1991); also, 8.6% of those under 13 years of age had tried cannabis.[81]

The US Substance Abuse and Mental Health Services Administration (SAMHSA) conducts an annual survey of the civilian, non-institutionalized population of the United States aged 12 years or older. This report, the National Survey on Drug Use and Health (NSDUH), presents national estimates of rates of use, numbers of users, and other measures related to illicit drugs, alcohol, and tobacco products.[82] In 2013, NSDUH showed that 24.6 million Americans aged 12 years or older were illicit drug users, meaning they had used an illicit drug during the month prior to the survey interview.[82] Marijuana was the most commonly used illicit drug, with 19.8 million past-month users (7.5% of those aged 12 years or older). There was also an increasing trend over time in the use of marijuana; from 2006 to 2013, the number of people using daily cannabis almost doubled.

Higher use is found in high-risk youth such as school dropouts, the homeless, and those in the juvenile system. A survey of juvenile detainees revealed a lifetime use of 54% and a daily cannabis use of 16%.[83] The prevalence of cannabis use disorders (*see below*) has recently increased in American veterans of war and was found to be highest in states that had medical cannabis.[84]

Cannabis and other drug use

One of the disturbing issues about cannabis use that clinicians need to know is that pot users typically combine cannabis with other chemicals to become polydrug users.[65] The human brain evolved over millions of years and one of its traits to ensure survival of *Homo sapiens* was to combine survival actions (i.e., eating and sex for procreation) and link these actions with pleasure. Drugs which induce euphoria (i.e., methamphetamine, heroin, cocaine, phencyclidine, nitrites, cannabis, and others) have overtaken this link for a negative purpose.

The devotion to this experience is reflected in the many *noms de plume* given to this drug, as noted previously, as well as to other illicit drugs. Cannabis produces such a pleasurable experience for its users that it often leads the smoker to seek a never-ending increase and/or prolongation of the euphoria at the expense of most or even anything else. This hijacking of the brain reward system by polydrug abuse leads to profound changes in the delicate adolescent central nervous system at biochemical, neuronal, and cellular levels, with devastating results for the abuser, the person's family, and for society from generation to generation.[1,65,85] The effects of cannabis on the central nervous system are reviewed later in this publication.

Polydrugs and cannabis

Research notes that substance use increases in many persons as they transition from adolescence to adulthood. Predictors of substance use include use of drugs in adolescence (i.e., junior high school or high school) and influence of peers; predictors of substance use in young adulthood include previous drug use, peer influence, and mental health factors (Table 5).[86,87] A key drug for many in this transition to the use of illicit drugs in young adulthood is smoking cannabis as an adolescent.[65] The concept that cannabis users also consume other drugs has been observed by clinicians and researchers for decades.[88–90] Clinicians caring for adolescents and young adults in all countries should screen these persons for polydrug usage to allow for early

Table 5
Risks for polydrug use and cannabis smoking (see text).

Cannabis smoking in adolescence (junior high or high school)
Peer influence
Mental health factors
Genetic factors
Chronic pain
Declining socioeconomic status from childhood to adulthood
Use of "Sherms"
Consumption of synthetic or designer drugs (spice drugs)
Intravenous marijuana use
Combination of tobacco and cannabis
Combination of cocaine and cannabis
Combination of alcohol and cannabis
Hookah use

identification of and potential intervention for such high-risk behavior.[1,65,91,92] Such behavior can occur in any youth including those with chronic illnesses such as diabetes mellitus.[93]

Genetic factors may also play an important role in the known link between cannabis use (especially when started in adolescence) and poly-illicit drug use as well as associations with depression, suicide, and psychosis (*see below*).[94] The polydrug use can follow a classic "gateway" model or "alternative" model.[95,96] A *national* study noted that 44.7% of persons with lifetime cannabis use went on to use other illicit drugs and that this was influenced by various sociodemographic factors as well as mental health disorders.[97] Another study in adult rats reported that inducing chronic THC use during the rat's adolescence increased its vulnerability to stress-induced relapse in heroin-seeking adult rates; their conclusion was that chronic THC exposure in adolescence leads to increased anxiety and risk of drug relapse in adulthood for humans.[98] A 13-year longitudinal cohort study in Australia noted that use of cannabis in young adulthood also predicts additional drug use.[99] A never-use history for cannabis was the strongest predictor for avoidance of other illicit drugs in young adulthood; quitting pot smoking reduced rates of illicit drug use, while more than weekly cannabis use had a two to three times rate of illicit drug use, and daily cannabis use was linked with six times the rate for cigarette smoking.[99]

Thus, a pot smoker may mix the marijuana joint with nicotine, opioids, cocaine, or hallucinogens (such as lysergic acid diethylamide or LSD) in attempts to enhance the euphoric effects of cannabis. Some may add cannabis to enhance the pleasurable time of other drugs of choice as well.[100] A cannabis joint can be hand-rolled or dipped into phencyclidine (PCP) dissolved in an organic solvent such as formaldehyde; this combination is smoked after drying and has been called "wet, Sherms, or water."

Cannabis users also consume synthetic cannabinoids in attempts to avoid drug detection and also to find a marijuana-like high.[101] Additives of the past include methaqualone and glutethimide. Cannabis users will also misuse prescription drugs including atypical antipsychotics.[102] These various additions contribute to the potential negative effects from such polydrug usage. The risk of syringe sharing among injection drug users was increased when they also smoked cannabis during the same day, even though this group was not regularly smoking cannabis.[103]

A study utilizing a case-crossover design reported that use of cannabis is a trigger for initiation of cocaine consumption even when genetic factors and environmental factors were held constant.[104] The association between cannabis and cocaine is well known and very dangerous for polydrug users.[105] The association between cannabis and 3,4 methylenedioxymethamphetamine (MDMA or ecstasy) is unfortunately also well known.[106,107] A French study of 90 persons with cannabis use disorder and average age of 27.5 years noted 41% lifetime history of cocaine use, 41% of benzodiazepines and hypnotics use, 40% of ecstasy use, and 23% of heroin use.[63] Intravenous drug use was noted in 4% of these persons with cannabis use disorder.[63]

Cannabis and tobacco

Individuals on cannabis also tend to smoke tobacco for various reasons, including similar cues of smoke seen in both the smokers, shared genetic issues, and withdrawal symptoms seen in both.[108] In a study of 467 adults with regular use of both tobacco and cannabis, it was reported that one-third initiated cannabis use before using tobacco, nearly 50% started using tobacco before using cannabis, and most pot smokers who ceased smoking tobacco did so after becoming regular cannabis smokers.[109] A French study of 90 persons with cannabis use disorder and average age of 27.5 years noted 99% lifetime history of tobacco use.[63]

Hookah use is associated with additional drug use including cannabis.[110] An identified risk factor for cannabis and tobacco consumption is declining socioeconomic position from childhood to adulthood.[111] A key point in counseling cannabis users is to encourage them to not only stop the pot use but also the often-found concomitant tobacco use.[112]

Cannabis and alcohol

Alcohol is a common drug taken with cannabis for heightened euphoria as well as sedation; adding diazepam or other benzodiazepines also increases the sedative effect. Individuals who take disulfiram because of alcohol dependence and add cannabis can note an augmentation of cannabis-induced psychoactivity because of THC blockage by the disulfiram.[65] Research notes that 45% of college students who illegally consumed prescription drugs also use cannabis, while 24–57% used alcohol.[113] A French study of 90 persons with cannabis use disorder and average age of 27.5 years noted 96% lifetime history of alcohol use.[63]

Cannabis consumption typically occurs after use of alcohol, though cannabis use may start first, and such a cannabis-before alcohol pattern is more commonly seen with African-American versus European-American persons.[114] Cannabis-associated problems are more common in African-American females versus European-American females.[114] Counseling of cannabis users should include not only advice to stop cannabis but also the often-found concomitant alcohol use, which may be at very high levels.[112]

Cannabis and pain medications

Research also notes that those seen in a pain clinic are at an augmented risk for cannabis consumption. A study of pain clinic patients looked at 21,746 urine specimens and reported cannabis (tetrahydrocannabinol) in 13% in contrast to 4.6% with cocaine and 1.07% with methamphetamine.[115]

Cannabis lab testing

Cannabis testing has been used to verify past cannabis use but not the presence of cannabis intoxication, dependence, or abuse. One may also find testosterone and luteinizing hormone (LH) suppression, though the precise meaning of such suppression is not clear. Positive urine testing for THC is not seen with passive cannabis inhalation nor does urine testing identify use of synthetic cannabinoids. Drug testing using high-performance liquid chromatography with diode-array detection can identify low THC content in cannabis seedlings right after germination; however, chemotype determination of THC can occur as the plant ages—at 3 weeks and beyond.[116]

THC–COOH (11-nor-9-carboxy-THC) is a key metabolite seen in blood or urine testing for cannabis identification. THC–COOH is the main secondary THC metabolite developed after taking cannabis and is not psychoactive; its testing is used to identify cannabis abstinence, and a positive test can be confirmed with gas chromatography–mass spectrometry THC blood testing—indicating recent cannabis exposure.

Plasma and whole blood testing can also identify 11-hydroxy-THC after cannabis consumption. Polymerase chain reaction (PCR) testing has been used by police to find out where specific cannabis samples originate as part of forensic investigations.[117] In addition to blood and urine testing for cannabis identification, saliva and hair testing can be done particularly for chronic cannabis consumption.[118,119]

Pharmacology of cannabis

Cannabis contains over 60 compounds known as *phytocannabinoids* that are the active constituents in addition to over 400 other chemicals such as the known carcinogen benzopyrene.[47,120] Another cannabis chemical group under study is the cannabis *terpenoids*: myrcene, α-pinene, linalool, limonene, β-caryophyllene, nerolidol, caryophyllene oxide, and phytol.[121] Cannabinoids have been classified into three subgroups including *phytocannabinoids*, *endocannabinoids*, and *synthetic cannabinoids* (Table 6).[122] A brief discussion of cannabinoid pharmacology is now provided.

Phytocannabinoids

Cannabinol was the first phytocannabinoid (plant derivative) to be isolated, followed by cannabidiol and then Δ^9-tetrahydrocannabinol (THC) in the 1960s.[47] THC has been demonstrated to be the primary constituent that contributes to the psychoactive properties of marijuana, while cannabinol and cannabidiol lack this ability.[122,123] Other phytocannabinoids include tetrahydrocannabivarin, cannabigerol, and cannabichromene.[121] Comments are provided here on THC and cannabidiol.

Δ^9-tetrahydrocannabinol (THC)

Research has primarily focused on THC but has been hampered by its chemical instability, Schedule I classification, un-standardized herbal preparations (medical marijuana), and inter-patient variability.[124,125] The chemical properties of THC include high lipophilicity; water insolubility; and sensitivity to heat, light, acid, and oxidation.[126–129] The most common routes of ingestion for THC include inhalation via cigarette or vaporizer and orally in baked goods or liquids (Table 3).[126]

Factors that influence the pharmacokinetics of THC include THC content, smoking duration, puff duration, inhalation volume, breath-holding, gastric acidity, and first-pass metabolism.[126,129] In a study by Davis et al.,[130] smoking characteristics were evaluated utilizing a smoking machine. It was found that ~16–19% of THC was found in mainstream smoke, ~30%

Table 6
Types of cannabinoids.

Phytocannabinoids
Cannabinol (CBN) (metabolite of THC)
Cannabidiol (CBD) (isomer of THC)
Cannabigerol (CBG) (alpha 2 adrenergic receptor agonist)
Tetrahydrocannabivarin (THCV; THV; TCH homolog)
Cannabichromene (CBC)
Endocannabinoids (endogenous cannabinoid agonists)
2-AG (2-arachidonoyl glycerol)
Anandamide (arachidonoyl ethanolamide)
Synthetic cannabinoids
Dronabinol (synthetic THC in sesame oil): Schedule III drug
Nabilone (schedule II drug)
Nabiximols (phytocannabinoid marketed in Canada)

was lost due to pyrolysis, and the remainder is likely lost in the sidestream smoke, cigarette butt, and partial lung absorption.[126,129,130] Pharmacokinetic details are noted in Table 7.

Peak plasma concentrations occur rapidly after inhalation and are delayed with oral administration.[128,131–134] Systemic bioavailability is relatively low for both oral and inhalation.[126,131,132] Occasional inhalation use, extensive first-pass metabolism, and erratic absorption produce lower bioavailability compared to heavy inhalation use.[126,129] THC is extensively distributed to tissues, especially fat, where it accumulates and is stored.[126]

The 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) metabolite penetrates and produces higher concentrations in the brain compared to THC.[126] THC undergoes hepatic metabolism via hydroxylation and oxidation, and high clearance rates have been associated with extensive first-pass metabolism.[126,132,133] THC is slowly eliminated from plasma due to redistribution from fat tissues and half-life for metabolites exceeds that of the parent compound.[126,132,133] Excretion is predominantly through the biliary tract and into the feces due to recirculation of metabolites through the liver and extensive protein binding.[125,134]

Urinary excretion of THC occurs as acid metabolites, and drug screening results can fluctuate with the last positive result occurring ~13 days for light users and ~32 days for heavy users.[126,135] A moderate correlation (oral and inhalation use) has been observed between plasma concentrations and the high euphoria associated with cannabis, but the peak psychotropic effects are often occurring while plasma concentrations are falling, and significant inter-individual variation is noted.[126,129,134]

Both THC and its active metabolite 11-OH-THC contribute to the psychotropic effects of cannabis. Common symptoms experienced by users include a mixture of stimulant and depressant effects. A review by Green et al.[58] describes self-reported symptoms including elevated mood, altered sensorium, relaxation, increased appetite, and enhanced insight as well as paranoia, depression, hallucinations, and anxiety. Tolerance has been associated with receptor down-regulation, and withdrawal syndrome can occur with abrupt discontinuation after long-term high-dose cannabis use.[126] Symptoms tend to be mild and can include restlessness, difficulty sleeping, sweating, diarrhea, weight loss, and irritability.[126]

Cannabidiol

Cannabidiol has anxiolytic and neuroprotective (antipsychotic) effects while potentially reducing the psychoactive effects of THC.[122,126,136] Thus, research has suggested that though the endocannabinoid system and its chemical components (i.e., cannabidiol) may be contributory to psychiatric conditions, it may also potentially be useful in amelioration of psychiatric conditions such as anxiety, depression, anorexia nervosa, and others (*see below*).[137] Cannabidiol can stimulate limbic and paralimbic areas of the central nervous system (CNS), leading to reduced autonomic arousal and feelings of anxiety.[138] This is in contrast to the anxiogenic effects of THC.

Cannabidiol has anticonvulsant, analgesic, anti-emetic, and anti-inflammatory effects.[122,124,136] Cannabidiol has not been shown to affect body temperature, heart rate, blood pressure, or gastrointestinal transit. Research has noted lower capacity of fertilization, reduced activities of

Table 7
Pharmacokinetics of delta-9-tetrahydrocannabinol (THC).[126,131–134]

Parameter	Inhalation	Oral	Intravenous
Time to peak plasma concentrations (avg)	3–10 min	60–90 min; up to 4–6 h	3–10 min
Bioavailability	18% (Range: 8–24%)[132] 23% Heavy users[131] 10% Light users[131]	6% (Range: 4–12%)	
Volume of distribution			10 L/kg
Plasma clearance rate (avg)			197–248 ml/min[133] 600–1000 ml/min[134]
Elimination half-life		25 h[133]	18–36 h[133,134]

p-glycoprotein as well as other drug transporters, and inhibition of hepatic drug metabolism.[136] Doses up to 1500 mg per day and chronic use of cannabidiol have been tolerated.[136]

Endocannabinoids

The endocannabinoid system consists of central nervous system receptors and their endogenous ligands, which are triggering molecules that bind to a target protein site.[139] This system is involved in processes of brain reward that are related to drug abuse, as noted by studies in humans and animals, which include cue-induced relapse of drug abuse.[140] Most drugs of abuse alter brain levels of endocannabinoids in which there are changes in the endocannabinoid control of mesolimbic dopamine behavior, leading to the need for more of these drugs.[141]

Cannabinoids interact through cannabinoid-1 (CB_1) and cannabinoid-2 (CB_2) receptors that are coupled to G-proteins.[123,142] CB_1 receptors are predominantly found in the brain (highest in the cortex, hippocampus, basal ganglia, and cerebellum) with lower concentrations in the peripheral tissues (the liver, testes, small intestine, etc.) and modulate the psychotropic effects of cannabis.[142] CB_2 receptors are mostly found on immune cells modulating immune function, including T cell proliferation, B cell action, and proinflammatory cytokine release.[142–144] Activation of these receptors results in adenylate cyclase inhibition and decreased cAMP as well as inhibition of select calcium channels and activation of mitogen-activated protein kinases (MAPKs).[122,142]

The two most widely studied endogenous ligands include anandamide and 2-arachidonoyl glycerol (2-AG), which interact with γ-aminobutyric acid (GABA) and glutamate neurotransmitter systems to modulate pain, cognition, movement, and emotions.[122,142,145] Production and release of these endogenous compounds are stimulus-driven, with rapid termination occurring via cellular uptake and enzymatic hydrolysis.[47,122,142] Typically, anandamide, like THC, has affinity for both CB_1 and CB_2 receptors, with greater efficacy at CB_1 receptors, producing a pharmacological profile analogous to THC.[125] Cannabidiol has no affinity for CB_1 or CB_2 but has been shown to positively influence the activity of anandamide.[146]

Synthetic cannabinoids

Two synthetic cannabinoid agents are currently available in the United States (US) and Canada and include dronabinol and nabilone (see Table 8 for characteristics). Dronabinol is a synthetic THC in sesame oil, while nabilone is a synthetic molecule similar to THC.[122] Due to nabilone's potency, it is a controlled substance schedule II versus schedule III for dronabinol.[147] Both are US Food and Drug Administration (FDA) approved to treat nausea and vomiting secondary to chemotherapy, while dronabinol also is labeled for human immunodeficiency virus (HIV)-associated anorexia.[141]

Dronabinol has poor bioavailability with only 10–20% of the dose reaching the circulatory system compared to nabilone, which has rapid and complete absorption through the gastrointestinal tract.[122,147,148] Both agents have active metabolites, but dronabinol's major metabolite, like THC, is 11-OH-THC, which contributes to its psychotropic effects.[121,147] Common side effects for dronabinol include sedation, dizziness, elevated mood, and abnormal thinking.[147] Nabilone has similar side effects but also produces a higher incidence of dry mouth and muscle incoordination.[125,147,148]

The other marketed product in Canada is nabiximols, which is actually a phytocannabinoid. A summary of the product is noted in Table 8. It contains equal parts of THC and CBD and is synthesized from two cannabis plant extracts.[149] The addition of CBD is thought to mediate the psychotropic effects of THC.[122] It is available as an oral mucosal spray that is self-titrated and is indicated for cancer pain, spasticity, and neuropathic pain related to multiple sclerosis (MS).[149,151]

Medical cannabis

As noted above, some cannabis-derived, synthetic products are currently available to treat a limited number of medical conditions. With the expanding knowledge of cannabinoid and

Table 8
Commercial preparations of synthetic cannabinoids.[122,147–149]

	Dronabinol	Nabilone	Nabiximols
Brand name	Marinol®	Cesamet®	Sativex®
	Synthetic cannabinoid	Synthetic cannabinoid	Phytocannabinoid
Chemistry	Pure synthetic THC in sesame oil	Synthetic molecule similar to THC	THC/CBD
Dosage form	Oral capsule	Oral capsule	Oral mucosal spray
Strengths	2.5, 5, and 10 mg	1 mg	27 mg (THC) and 25 mg (CBD)
Availability	US and Canada	US and Canada	Canada
Controlled substance schedule	Schedule III	Schedule II	CDSA II
Indications	Anti-emetic and AIDS associated anorexia	Nausea and vomiting due to cancer chemotherapy	Cancer pain, spasticity, and neuropathic pain associated with MS
Initial dose	Anorexia: 2.5 mg twice daily Anti-emetic: 5 mg/m^2 every 4–6 h	1–2 mg Twice daily	1 Spray twice daily
Maximum daily dose	Anorexia: 20 mg/day Anti-emetic: 15 mg/m^2/dose	6 mg In three divided doses	$\leq$ 12 Sprays per day
Contraindications	Hypersensitivity to dronabinol, marijuana, cannabinoids, any other component or sesame oil, individuals with history of schizophrenia	Hypersensitivity to cannabinoids, nabilone, or any other component	Cannabinoid hypersensitivity, serious CV disease, history of psychotic disorders, childbearing age women not using birth control, pregnancy, breast-feeding, and males intending to start a family

THC: tetrahydrocannabinol; CBD: cannabidiol; US: United States; AIDS: acquired immunodeficiency syndrome; MS: multiple sclerosis; CV: cardiovascular.

endocannabinoid pharmacology, additional targets for drug development may include selective CB_2 agonists, cannabinoid receptor agonists that do not readily cross the blood–brain barrier, modification of endocannabinoid cellular uptake or enzymatic hydrolysis, and CB_1/CB_2 antagonists.[47] These strategies may help to overcome some of the challenges associated with THC, minimize its psychotropic as well as dependency-inducing effects, and expand the number of conditions that potentially could be treated via modification of the endocannabinoid system.

The endocannabinoid system is involved in many functions including emotions, memory, movement, cell proliferation, brain reward system, and others.[140,150] Thus, it is critical to ask if research can accurately tease out which of these cannabinoids and related chemicals may be useful in safely treating human disease, as noted in Table 8. The key question arises whether we can safely expand the use of these products to other conditions, as noted in Table 9. Research on smoked, vaporized, and oral cannabis products for potential improvement of health is continuing.[151] This section briefly use of cannabis products for management of selective diseases.

Cancer

As noted in Table 8, dronabinol and nabilone can be used as anti-emetics in those undergoing chemotherapy, though they are not typically used as first-line agents.[152,153] Cannabinoids are under research for overt cancer treatment, since there is indication that these chemical compounds can inhibit cancer growth, angiogenesis, and metastasis.[154,155] However, current studies on the use of cannabinoids to treat cancer are contradictory, and potential use of cannabis products must wait for more research in this century.[156–158] Nabiximols oral spray is indicated for pain due to cancer. There is no scientific evidence for the safe use of the marihuana plant itself via smoking for cancer treatment or as an anti-emetic in chemotherapy.

Table 9
Diseases/conditions targeted by research on cannabis-derived products (see text).

Anxiety
Anorexia (i.e., in HIV/AIDS)
Atherosclerosis
Brain infarction (size reduction)
Cardiac reperfusion injury
Chronic pain (including neuropathic pain)
Crohn's disease (i.e., diarrhea)
Depression
Dystonia
Emesis and nausea with chemotherapy (FDA approved)
Epilepsy
Glaucoma
Hypertension
Huntington's disease
Inflammatory bowel disease (i.e., anti-diarrheal effects)
Multiple sclerosis (i.e., spasms)
Post-stroke management
Posttraumatic stress disorder (blocking negative memories)
Prostate carcinoma (adjuvant treatment)
Psychosis
Treatment for rheumatoid arthritis
Others

Epilepsy

Research has noted that cannabidiol and Δ9-tetrahydrocannabinol can have anticonvulsant effects in animal models, though proconvulsant effects can be seen as well.[153,159–161] Non-controlled anecdotal reports of improvement in epilepsy have been reported particularly in severe, medication-resistant epileptic conditions such as Dravet and Lennox–Gastaut syndromes.[161–163] Some suggest that cannabis products may offer benefit in severe epilepsy and other neurological conditions when standard care (i.e., currently approved anticonvulsant medications) is not helpful.[164]

Unfortunately, the current status of research, according to a 2014 Cochrane Database System Review, is that there is no scientific evidence that cannabinoids are effective in humans with epilepsy nor can the long-term use or safety of this product be established at this time.[165] A 2014 report of the American Academy of Neurology notes that oral cannabinoids are of unknown efficacy in epilepsy.[166] There is no evidence that smoking the cannabis plant is safe or effective in epilepsy.[164,166] More well-designed research is recommended and is underway in this arena.[167,168]

Multiple sclerosis

Nabiximols [oromucosal spray of tetrahydrocannabinol (THC) with cannabidiol] is approved for adult patients with multiple sclerosis (MS) who have moderate to severe spasticity that has not improved with other antispasticity drugs.[169–172] Research has also noted that smoked cannabis can relieve spasticity in MS as well.[173]

Other neurological conditions

Though there are anecdotal reports that headaches and other types of pain (including chronic pain) can be helped with cannabis products, more research is needed to establish such use.[174–176] Though there is no clear research support for use of cannabis products in adults with Tourette

syndrome, anecdotal reports occur of improvement in tics as well as behavioral issues despite tic improvement with first-line anti-tic medications.[166,177]

There is no research to support the use of cannabis products for non-chorea-related symptoms of Huntington disease or levodopa-induced dyskinesias of persons with Parkinson disease.[166] A study revealed improvement in sleep and pain scores in persons with Parkinson disease who smoked cannabis.[178] Research on potential neuroprotection for those with traumatic brain injury and Alzheimer's disease continues, but more research is needed on which cannabis products may be helpful and how they should be given.[179,180] Research is also looking at the use of cannabis for neonatal hypoxic–ischemic encephalopathy.[161]

Neuropsychiatric disorders

Studies also continue on potential neuroprotection from cannabidiol and other cannabis products for patients with addiction, schizophrenia, and anxiety.[181–189] Despite potential benefit from such products in psychiatric disorders, more scientific research (i.e., well-powered, double-blind, randomized, controlled trials) is needed to identify the role of which cannabis products may be of benefit in specific situations and with respect to currently available pharmacologic agents; the long-term consequences of such treatment must be ascertained as well.[161,190,191]

Miscellaneous

Though use of dronabinol can reduce intraocular pressure, endocannabinoids and the cannabis plant are not recommended as treatment of glaucoma.[192] Dronabinol is indicated for anorexia in HIV/AIDS persons and has been used in HIV-associated neuropathic pain; however, there is limited data supporting the efficacy and safety of cannabis smoking in those with this condition.[163,193] Studies of cannabis in persons with sleep disorders are mixed and require more research to identify potential benefit.[190,194] Though individuals with gastrointestinal disorders anecdotally report benefit from cannabis, research remains limited in this area.[195–197]

Current status: Medical marijuana

The United States Food and Drug Administration (FDA) approved dronabinol capsules on May 31, 1985, for management of nausea and emesis that is associated with cancer chemotherapy (Table 9). The US FDA approved dronabinol on December 22, 1992, for management of anorexia associated with weight loss in persons with AIDS. Oral nabilone was also approved by the FDA on December 26, 1985, for use in management of nausea and vomiting associated with cancer chemotherapy. In Canada and other countries, the oromucosal spray nabiximols is indicated for management of cancer pain as well as spasticity and neuropathic pain associated with multiple sclerosis.

As reviewed (*see above*), there are a number of anecdotal reports of improvement in other conditions with use of cannabis products including limited studies on the use of smoking the cannabis plant for medical conditions. What should clinicians tell their patients in 2015 about the use of smoking cannabis for recreational use and for treatment of medical or mental health issues? Clinicians must note that there are few indications for use of oral dronabinol and nabilone that are FDA approved. Before clinicians go "off-label" and prescribe treatments that are not approved, it is best, as with all products, to carefully look at the potential side effects of smoking this plant. One should weigh risks of adverse effects versus credible research suggesting possible benefit. The very serious issue of polydrug use by many cannabis smokers has already been addressed. The growing phenomenon of viperous cannabinoid designer drugs is now considered, followed by a discussion of potential adverse effects from consuming the cannabis plant.

Cannabinoid designer drugs

Modern chemistry has provided recreational cannabis consumers with a variety of designer drugs ["new psychoactive substances (NPS)" and "smart drugs"] that were developed in the 1960s and now include cannabinoid designer drugs (synthetic cannabinoid receptor agonists) that have been identified since 2008 and given a variety of colorful names such as "spice drugs," "legal highs," "K2 drugs," or "Kronic."[198–201] These synthetic cannabinoids or cannabimimetics have effects that are similar to smoking the cannabis plant, as they bind to the same cannabinoid brain and peripheral organ receptors as THC.[202–209]

These psychoactive products contain exotic names such as *Spice Gold, Yucatan Fire*, and more than 140 products.[202,210] They are typically found in head shops (retail outlets) or on the internet and sold as air fresheners or incense; they contain the warning "not for human consumption" or "for aromatherapy only" so they can be "legal" products.[210–213]

Though they do not resemble the chemical structure of THC, they have up to 10 times the strength of delta-9-THC due to being potent agonists of cannabinoid receptors 1.[203,210,214,215] Toxicology screens for THC often miss the consumption of these cannabinoid designer drugs.[204,208] These cannabimimetics contain various chemical structures and are developed by underground or clandestine laboratories who have hijacked the legitimate idea of developing more selectivity for cannabinoid receptors CB_1 and CB_2 for medical use.[216] They are typically indole- and pyrrole-derived synthetic cannabinoids, and their differences from classical cannabinoids are under active study.[217]

As soon as one product is banned, the makers of these drugs make another variation and keep ahead of the local laws. They may be marked as being "safe," since they are tobacco and cannabis free, but they can lead to similar unwanted cannabis effects such as withdrawal symptomatology, intoxication, anxiety, tachycardia, increased blood pressure, tremors, seizures, hallucinations, paranoia, suicidal ideation, cognitive impairment, psychosis, acute kidney injury, and death.[202,208,218–222] Maternal use of these drugs may impair fertility and pregnancy.[223]

A variety of chemicals can be added during the production phase, leading to additional potential complications. Thus, one may not know what is in these products or if the adverse effects are due to the cannabimimetics, added impurities, or both.[224] Current evidence suggests these are very dangerous chemicals and they do not represent a safe alternative to cannabis neither recreationally nor medically.[225]

Medical adverse effects of cannabis

Clinicians should know that cannabis smokers are facing a large number of potential adverse medical and other negative effects. Table 10 lists some of these adverse medical issues as well as other potential cannabis effects in pregnancy, poisoning, sports doping, and motor vehicle accidents (MVAs). As noted by Galen in the first century, consumption of cannabis can have adverse effects that have been more clearly identified over the past several decades starting in the 1960s and 1970s.[226–237] As patients are seen with various health problems, clinicians should screen for drug use including cannabis (*see below*). Adverse effects can vary widely between persons based on a variety of factors including genetic influences, personality characteristics, THC potency, and others.[238] Clinicians should keep this in mind for all patients including the Greatest Generation and the Baby Boomer generation who may turn to cannabis in attempts to relieve various geriatric ailments but not realizing more falls and injuries may await them as a result.

Cardiovascular adverse effects

Some cannabis smokers are at an increased risk for adverse cardiovascular effects (Table 11).[239–241] Cannabis consumption leads to stimulation of cannabinoid receptors (i.e.,

Table 10
Potential adverse medical and other effects of cannabis smoking.

Cardiovascular
Pulmonary
Carcinogenic
Gastrointestinal (cannabis hyperemesis syndrome)
Dental
Miscellaneous
Pregnancy and cannabis
Cannabis poisoning
Sports doping and cannabis
MVAs and cannabis

CB_1 and CB_2) that are found throughout the circulatory system.[241] Cannabinoids have varying, complex effects on blood pressure, and cannabis can acutely lead to an increase in heart rate as well as an increase (typically mild) in blood pressure followed by a reduced, vascular, resistance-induced orthostatic hypotention.[226,239,240] Increasing anecdotal cases are being reported in cannabis smokers which include cannabis arteritis, cardiomyopathy, myocardial infarction, sudden cardiac death, transient ischemic attack (TIA), cerebrovascular accident (stroke), and cardiac arrhythmias (Table 11).[241–249]

The association of these various complications with cannabis versus cannabis and tobacco use is difficult, since cannabis smokers often smoke tobacco as well; thus, the cannabis lifestyle may be the critical piece in increasing the risk for TIA and stroke.[250] In a study of 113 non-diabetic patients with premature peripheral arterial disease (i.e., diagnosis under the age of 45 years), cannabis smoking seemed to be a risk factor for thromboangiitis obliterans.[251]

Though the term "cannabis arteritis" is not accepted by all researchers, pending more studies, it is well known that cannabis has vasoconstrictor activity that can lead to adverse effects in some individuals.[252,253] The link of cannabis smoking and arteritis has been seen for several decades, including the use of *Cannabis indica* that was reported in 1960.[254,255] Some authors have noted that multifocal angiopathy seen in cannabis smokers may be an important factor in the development of ischemic stroke in young adults.[256,257] In another study, strokes in cannabis smokers occurred mostly in the posterior cerebral circulation in young males who often had unilateral disease in their lower limbs at the time of their presentation.[258] Cerebral and myocardial infarction in young adult cannabis consumers has become a known phenomenon.[259]

In a report of 4 young males with arteritis in cannabis smokers of at least 4 years' duration, distal pulses were absent and there was persistent distal necrosis.[260] In three of these patients, improvement was seen with cessation of the cannabis along with basic arteritis management; in the fourth patient who continued cannabis smoking, limb amputation occurred.[260] A predilection for the basal ganglia has been reported in young adults who smoke cannabis and develop an ischemic stroke.[261] Synthetic cannabinoid use can also lead to ischemic stroke in young adults.[262]

Anecdotal cases of ST-segment elevation mimicking the Brugada syndrome have been reported in cannabis smokers.[244,263–265] Atrial fibrillation has also been reported in cannabis users.[264] Cannabis smoking can increase risks for coronary heart disease and should be avoided

Table 11
Potential adverse cardiovascular effects of cannabis smoking (see text).

Arteritis
Cardiomyopathy
Myocardial infarction
Sudden cardiac death
Transient ischemic attack (TIA)
Cardiovascular accident (CVA and stroke)
Cardiac arrhythmias

in such persons.[239,265] Anecdotal cases of myocardial infarction in cannabis smokers are well known in the literature, with an increased risk within 1 h of cannabis smoking.[239,258,266,267] Periods of cardiac asystole were noted on a 24-h Holter monitor in a 21-year-old person with congenital heart disease due to cannabis inhalation.[268] Sudden death can occur in persons on illicit drugs, and in such an individual with a history of cannabis use and positive urine cannabinoids, the plasma THC level should be measured before linking the sudden death to cannabis effects.[269] The increased risk of precipitating a myocardial infarction is seen for 2 h after cannabis smoking.[269] Finally, negative effects of cannabis on those with cardiovascular disease are well known.[270]

Pulmonary adverse effects

Clinicians should also know that there are considerable pulmonary adverse effects noted in some cannabis smokers. Advice to patients should be to avoid cannabis, but if a person must smoke marijuana, occasional and low cumulative cannabis use is the safest. For example, a study of 5115 adult males aged over 20 years concluded that such low use was not associated with negative effects on pulmonary function due to suggested anti-inflammatory effects.[271] Cannabis consumption, however, is typically not occasional nor characteristic of low accumulative cannabis use, and potential negative pulmonary effects are a threat to these smokers who often consume tobacco as well.

Both cannabis and tobacco contain a toxic collection of gases and other chemicals that can be injurious (toxic) to the pulmonary system.[272] Cannabis smoke has polycyclic aromatic hydrocarbons and carcinogens at increased levels than seen in tobacco smoke.[273] Techniques of cannabis smoking may deliver more cannabis particulate matter into the lungs than even found with smoking tobacco.[272] Aluminum in cannabis and tobacco smoke accumulates in lung fluids, which increases the content of this metal in body tissues and can contribute to respiratory and neurological adverse effects in these smokers.[274] Pot smoking continues in those with cannabis dependence even with chronic cough, and combining this with tobacco leads to well-known tobacco adverse effects.[1,57]

Cannabis use leads to bronchodilation, and regular or heavy use leads to generalized airway inflammation with respiratory epithelial cell injury and injury to alveolar macrophages with cytokine and nitric oxide impairment as well as potential pulmonary infection as a result.[272,275] There is a dose-related large airway impairment that involves hyperinflation and airway obstruction; one cannabis joint may be equivalent to 2.5–5 cigarettes with regard to such pulmonary damage.[276] Cannabis smokers typically have more carbon monoxide and tar exposure than seen with cigarette smokers in an effect unrelated to THC potency.[277] The mixture of cannabis and tobacco in a cigarette is more toxic to the respiratory tree than tobacco alone.[278]

Chronic and/or heavy cannabis smokers may develop chronic cough, bronchitis, bullous emphysema (COPD: chronic obstructive lung disease), pneumothorax/pneumomediastinum, pulmonary dysplasia, pulmonary tuberculosis, and other respiratory infections (Table 12).[272,278–284] Cannabis alters the antibacterial and fungicidal activity of alveolar macrophages.[272,276] Individuals who use a shared cannabis water pipe have increased risk for pulmonary tuberculosis; *hotboxing* (cannabis smoking in a closed car with peers) can also lead to a tuberculosis outbreak.[280–282]

Consuming cannabis smoke that has fungal sports can result in pulmonary aspergillosis or other pulmonary infections from inhaled molds in persons with immune deficiency that can be potentially fatal.[285–287] Inhalation of marijuana adulterated with talcum dust can lead to a granulomatous lung inflammation called talcosis, which is a rare form of pneumoconiosis.[288] Dust disease was noted in hemp workers several decades ago.[289–291] Anaphylaxis to hemp seed ingestion has been described.[292] The increased airway resistance and large airway inflammation seen in cannabis users suggest causal though not proven links to COPD or macroscopic emphysema.[50,63-66,276,293–296] Smokers of both cannabis and tobacco have increased risks for abnormal tracheobronchial histopathology and COPD.[66,296]

Table 12
Potential adverse pulmonary effects of cannabis smoking (see text).

Allergic hypersensitivity
Chronic cough
Bronchitis
Bullous emphysema (COPD: chronic obstructive pulmonary disease) Pneumothorax/pneumomediastinum
Pulmonary dysplasia
Pulmonary tuberculosis
Other respiratory infections
Dust disease (talcosis) in hemp workers

Allergic hypersensitivity to cannabis, as detected by cannabis skin tests and IgE levels, may be seen in cannabis smokers; such patients may also be sensitized to tobacco and tomato.[297–302] Death in a 19-year-old male was reported; he consumed cannabis using a homemade water pipe ("bang"), which led to fatal alveolar hemorrhage probably due to acid anhydrides released from incomplete combustion of the marijuana in contact with homemade plastic material.[303] Smoking cannabis cut with micro-particles of silicon dioxide can lead to hemoptysis.[304] Pulmonary embolism has been reported in a 22-year-old smoker of both cannabis and tobacco.[305] Respiratory depression has been reported with use of synthetic cannabis, and two cases have been noted of respiratory depression from synthetic cannabis that required intubation management.[306]

Summary: Pulmonary effects

The toxic damage from tobacco seems to be worse than from cannabis, and cannabis smokers should be taught to avoid smoking tobacco.[307] Clinicians should teach cannabis smokers about the potential harmful effects of smoking cannabis on respiratory tissue and that cessation of this drug can reduce cannabis-induced pulmonary damage.[278,279] For example, chronic bronchitis seen with regular cannabis users subsides with the cessation of cannabis smoking.[307]

Cessation of cannabis smoking is best and should not be complicated by smoking tobacco as well. If cannabis smoking is to continue, it should be at a low dose in an intermittent fashion to reduce potential toxicity to the pulmonary system, which includes increased cough, sputum production, bronchitis symptoms, large airway inflammation, increased airway resistance, and hyperinflation (Table 12).[1,243,283,293,294,307–309]

Cannabis and cancer

As noted, cannabis smoke contains toxic chemicals in amounts similar to or higher than noted with tobacco, and cannabis smoke typically is inhaled more deeply than tobacco smoke; this delivers higher amounts of these toxins than tobacco smoking does.[310] Some research has linked chronic inflammatory and precancerous airway changes in cannabis smokers in a dose-dependent relationship along with an increase in airway cancer.[311] The literature suggests more of a link between lung and upper airway cancer from heavy or chronic cannabis smoking.[312]

Anecdotal reports are seen of upper and lower respiratory airway cancers in cannabis smokers.[280,312] A case of small cell lung cancer, for example, was reported in a 22-year-old male with a history of smoking one cannabis joint three times a week for 3 years.[313] Another case of small cell lung cancer was reported in a 26-year-old male with considerable cannabis exposure.[314] However, a proven link between cannabis smoking and lung cancer apart from comorbid tobacco smoking remains controversial at this time.[293,295]

Though some epidemiologic data gives an independent role of marijuana smoking to lung cancer development, current literature suggests that cannabis-only smokers remain at a lower risk of lung cancer than that seen with tobacco-only smokers or tobacco–cannabis smokers.[315–317] A study in Sweden of 49,321 males aged 18–20 years in 1969–1970 followed them through 2009; it concluded that, using Cox regression analyses ($n = 44{,}284$), heavy cannabis use (i.e., lifetime use of over 50 times) resulted in a twofold risk for developing lung

cancer over this 40-year follow-up period versus the risk due to tobacco and alcohol use.[318] Other research supports a doubled risk of lung cancer for cannabis smokers based on epidemiologic research, cellular research, and studies in animals as well as humans.[273]

Adverse gastrointestinal effects

Cannabis hyperemesis

Cannabinoid hyperemesis syndrome (cannabis hyperemesis syndrome) was first described in Australia in 2004 and is a cycle of emesis (cyclical vomiting complex) seen in some cannabis smokers.[319] It typically presents with intractable emesis (sudden, severe, and cyclic) in association with abdominal pain and a history of chronic cannabis smoking.[320,321] Though cannabinoids have been used to manage nausea and emesis, a paradoxical effect is seen in this emesis complex with three phases: prodromal, hyperemetic, and recovery.[322] The hyperemesis phase usually resolves within 60 h.[322]

Some noted temporary symptomatic improvement may occur with prolonged bath exposure or hot showers; thus, some researchers add compulsive hot water bathing as a part of this complex.[320,323–327] The differential diagnosis includes cyclic vomiting syndrome, psychogenic vomiting, bulimia nervosa with emesis, or "drug-seeking" behavior.[322,328] An extensive evaluation may occur before this diagnosis is made.[329]

The cannabinoid hyperemesis pattern resolves with intravenous fluids, anti-emetics, and cannabis cessation. Though anti-emetics may not be helpful in many cases, haloperidol has been used for management of the emesis complex with good results in a case report.[330] The hyperemesis complex can occur again with resumption of cannabis smoking.[322,324,331]

Miscellaneous gastrointestinal

Chronic cannabis smoking is associated with visceral obesity and adipose tissue insulin resistance but not hepatic steatosis or glucose intolerance.[332] Proven adverse endocrine effects of cannabis have not been identified.[333] Though drug-induced pancreatitis is usually linked to alcohol abuse, rare cases of pancreatitis have been reported in persons on cannabis, including recurrent acute pancreatitis.[334–336] A report was on a 22-year-old male with epigastric pain, nausea, and emesis.[336]

Cannabis body packing, done in attempts to illegally smuggle illicit drugs into a country, can lead to abdominal pain from colonic perforation and resultant peritonitis.[337] Extensive imaging of these body packers may be needed, and a "double-condom sign" (rectangular-shaped high-density shadows with a surrounding gas halo) may be seen on radiographs and computed tomographies (CTs) of cannabis and cocaine body packers.[338]

Dental effects of cannabis

Clinicians should know that cannabis smokers have an increased risk for impaired dental health that includes dental caries, oral infections, gingivitis, xerostomia, uvulitis, nicotinic stomatitis, leukoedema, and periodontal disease (Table 13).[339–348] Gingival enlargement may occur similar to that seen with the use of phenytoin.[57] Management of patients on cannabis is challenging, with an increased risk for patient problems such as anxiety, dysphoria, and prolonged tachycardia after local anesthesia with epinephrine.[339,341] Poor dental health can complicate overall medical health in cannabis smokers.

The oral mucosa of cannabis smokers can contain dysplastic changes and premalignant lesions.[339,349] Smoking cannabis and/or tobacco causes contact with many carcinogens (pro-carcinogens) such as polycyclic aromatic hydrocarbons.[350] Polydrug use complicates this picture, as cannabis smokers also use tobacco and alcohol, which increase exposure to carcinogens and the risk of oral squamous cell carcinoma, which represents 95% of oral malignancy.[350]

Table 13
Potential adverse dental effects of cannabis smoking (see text).

Dental caries
Dental dysplasia
Gingival enlargement
Gingivitis
Leukoedema
Nicotinic stomatitis
Oral infections
Periodontal disease
Poor dental health
Uvulitis
Xerostomia

Pregnancy and cannabis

Cannabis is the most widely used illicit drug by women of childbearing age; 15% of women aged 18–25 years report using cannabis.[351–353] Rates of reported use of cannabis by pregnant women range from 10% to 15% in predominantly middle-class samples to 23–30% in predominantly inner-city samples.[351–353] Clinicians should tell their patients that cannabis smoking during pregnancy can lead to behavioral consequences for offsprings (Table 14).

Fried[351,352] has reported extensively on the effects of cannabis use during pregnancy and its neurobehavioral outcomes. The findings are based on two large studies: the Ottawa Prenatal Prospective Study (OPPS) and the Maternal Health Practices and Child Development Study (MHPCD).[351,353]

Since 1978, the OPPS has been investigating the effects of cannabis and tobacco inhaled during pregnancy. The sample consisted of low-risk, white, predominantly middle-class families and was representative of the English-speaking Ottawa population. The investigators followed 180 offsprings from neonatal period to young adulthood. The MHPCD study was started in 1982 and has investigated the effects of prenatal use of cannabis, alcohol, and cocaine.[352] The study population consisted of high-risk, low socioeconomic status, predominantly African-American women in Pittsburgh.

Findings from the OPPS and the MHPCD and other similar cohort studies suggest that the effects of cannabis use during pregnancy on fetal growth and central nervous system are moderated to some extent by other associated risk factors that may impact the outcomes. None of the studies showed any morphological abnormalities in newborns. Fetal and immediate postnatal growth is minimally affected. No adverse effects on growth or behavior were reported through the toddler years. The initial indication of adverse effects of prenatal cannabis use was noted first after 3 years of age, with main impact on the executive function. The effects are seen as increased inattention and impulsive behaviors. There is also difficulty in problem solving,

Table 14
Potential adverse effects of cannabis smoking during pregnancy for offsprings (see text).

Low birth weight
Preterm labor
Small for gestational age
Treatment in a neonatal intensive care unit
Childhood effects
Inattention problems
Problem-solving problems
Aggression
Executive function dysfunction
Problems with memory and processing information
Depressive symptoms

especially in situations that require integration and manipulation of basic visuoperceptual skills. Problems with executive functioning persist through adolescence and young adulthood, as shown by long-term follow-up over 20 years.

Other research has also noted negative effects on the offsprings of mothers who smoke cannabis during pregnancy that extends into adolescence (*see below*).[354] Some research notes that the children of mothers who used cannabis during pregnancy have increased risks for impaired brain function with reduced executive functioning, memory, and processing of information.[355,356] Another study linked the use of cannabis during pregnancy to increase in aggressive behavior and attention dysfunction in offsprings, which was seen as early as 18 months of age in females.[357] Additional research links prenatal cannabis exposure to depressive symptoms in offsprings at 10 years of age.[358]

A report in Australia looking at pregnancy outcomes in females using cannabis revealed an association between cannabis and low birth weight, preterm labor, small for gestational age, and treatment in a neonatal intensive care unit; a multivariate analysis was done that controlled for use of tobacco, alcohol, and other illicit drugs.[355] Research has also suggested that cannabis smoking in females who breastfed increases risks for motor impairment in their children by 1 year of age.[359] Thus, females should be counseled to avoid cannabis use during pregnancy and lactation.[351–360]

Cannabis poisoning

The famous Greek physician to the Romans in the first century, Claudius Galenus (130–210 AD) wrote about marijuana poisoning seen in Roman citizens who consumed too much of this drug from eating it.[1,57] Also known as Galen of Pergamon, his writing was an early warning about cannabis acting as a poison to *Homo sapiens*, with increasing articles in this regard noted from various countries during the past half century. Clinicians must educate parents and society that cannabis poisoning can occur and to keep this plant away from children.

Christozov[361] wrote about cannabis poisoning in 1965 in Morocco, while Gourvès[362] reported a case of coma from Cannabis sativa in 1971—both of these articles were in the French literature. Hervás et al.[363] published about hashish poisoning in children in Spain, and Debray et al.[364] detailed the cannabis poisoning of a 13-month-old girl both in 1987. Lonka and Peterson[365] wrote about acute cannabis poisoning in Denmark in 1987.

Macnab et al.[366] reviewed 6 children in 1989 from British Columbia, Canada, with cannabis poisoning, three of whom presented in coma. The presentation included sudden drowsiness, pupil dilation, hypotonia, lid lag, and small leaves or granules in the mouth.[366] An article from the Netherlands in 1989[367] discussed acute neurological symptoms in a 14-month-old girl whose urinalysis revealed cannabis products, while an article from Italy in 1994 detailed acute cannabis poisoning of a 20-month-old infant.[368] Another article from Switzerland in 1997 discussed gastrointestinal and psychological effects from cannabis poisoning in four individuals who ate salad prepared with hemp seed oil.[369]

Cannabis cookies are becoming more popular as cannabis is being increasingly accepted in society, and one can expect to see more cases of coma in young children from ingestion of such eatable cannabis products.[370] Unfortunately, cannabis-induced coma has become a well-reported phenomenon.[371] Altered consciousness in an infant exposed to cannabis smoke via passive inhalation has been reported.[372] An 11-month-old girl with cannabis poisoning was reported in 2006 as the youngest victim from coma-induced cannabis ingestion.[373] Such incidents should be reported to the child protective services even though the ingestion may be considered “accidental”; the purpose is to prevent further danger to the child.[374]

In 2012, a 10-month-old infant was identified who had consumed oral cannabis and was seen for cannabis poisoning that included drowsiness, generalized hypotonia, restlessness, and elevated blood pressure; the urine was positive for cannabis.[375] Seizures and ataxia can also be seen in pediatric cannabis poisoning in addition to prolonged coma.[376,377] Flumazenil has been used for coma reversal in cannabis-induced coma in children.[378] Lethal cannabis intoxication is possible and has been reported.[379,380]

A French study in 2009 from the Marseille poison center from 1993 to 2007 revealed 93 cases of cannabis poisoning in persons under 18 years of age, 86% of whom were under 3 years of age (Table 15).[381] Most cases were due to hashish ingestion that belonged to one of the parents in the house. Clinicians should tell their patients that nearly all cases of cannabis poisoning occurred in the child's home and that cases are increasing in frequency.[381]

Unfortunately, cannabis poisoning is become a well-known pediatric problem in contemporary society that can lead to serious adverse reactions in children.[381,382] Rates of pediatric exposures to cannabis reported to the National Poison Data System increased from 2005 to 2011 in states that legalized marijuana in the United States.[383] Even the family dog is not safe with cannabis in the house, as canines who consume oral marijuana may become poisoned and even die from consuming too much cannabis.[384] Fatal cannabis poisoning has been reported in young adults.[385,386]

Miscellaneous adverse effects

Negative reactions to cannabis can occur in a dose-dependent and/or idiosyncratic fashion as well as the level of experience with this drug for some persons.[338,387] As with other drugs that induce altered states of consciousness, negative idiosyncratic reactions ("bad trips") to cannabis may occur due to anticholinergic effects that can include anxiety, terror, and psychosis.[387] Genital depersonalization ("Koro") has been reported in individuals after smoking cannabis.[388–390]

A variety of additional adverse effects can be seen with cannabis smoking, such as irritation of various structures (i.e., conjunctivae, nasopharynx, and bronchi), leading to injected conjunctivae, chronic cough, sinusitis, pharyngitis, and (chronic) bronchitis.[343] Adolescents and adults who present with chronic cough should be screened for cannabis use in addition to others in the classic differential diagnosis of respiratory infections, gastroesophageal reflux, and asthma.[391,392] A well-known result of smoking cannabis can also be weight gain from overeating combined with decreased exercise.[1,57] Acute effects of cannabis include rapid eye movement (REM) suppression and diffuse slowing of background electroencephalographic (EEG) activity.[1,57]

Intravenous injection of cannabis products can lead to severe, potentially lethal consequences.[393,394] A report in 1968 noted collapse after intravenous use of hashish.[393] A case report in 1976 identified two persons who injected cannabis intravenously and developed low blood pressure, renal insufficiency, thrombocytopenia, and rhabdomyolysis; this condition was reported as reversible without permanent sequelae.[395] Intravenous use of Δ-9-tetrahydrocannabinol (THC) and phytocannabinoids have been used in research for 40 years to study the effects of cannabis with particular reference to the development of mental illness.[396,397] Recent research has noted that intravenous THC can lead to paranoia in persons under study.[398]

A report of four youths who intravenously injected aqueous cannabis seed tea states that it led to fever, chills, cardiovascular effects (i.e., hypotension, tachycardia, and hypovolemic shock), gastrointestinal effects (i.e., nausea, emesis, abdominal pain, watery diarrhea, gastrointestinal bleeding, jaundice, and splenomegaly), neurologic effects (i.e., arthralgia, myalgia, and motor weakness), and non-oligemic renal failure.[399] All of these youths recovered over some weeks.[399]

Table 15
Cannabis poisoning: 93 cases (see text).[381]

(1) Marseille poison center report from 1993 to 2007
(2) 93 Cases of cannabis poisoning under 18 years of age
(3) 86% Were under 3 years of age
(4) Most cases due to hashish ingestion
(5) Nearly all cases due to cannabis in the child's home
(6) The cannabis belonged to the parents!
(7) Summary: protect the children in the home!

Individuals smoking cannabis can develop severe Raynaud's phenomenon, acne, rosacea, and psoriasis.[400] A case of priapism has been reported in a 22-year-old male with sickle cell trait who smoked cannabis.[401] As the geriatric population turns to cannabis to ease their aches and pains, there are increasing numbers of cannabis-related falls with injuries being reported in these seniors.[402] Clinicians should also know that use of synthetic cannabinoids is not safe and can lead to various adverse effects, causing emergency visits to hospital emergency rooms, including breathing problems as well as psychological problems (i.e., anxiety, panic, and paranoia) (*see above*).[403] Psychological/psychiatric adverse effects of cannabis are reviewed later in this review (*see above*).

Sports doping and cannabis

Smoking pot is not an action that improves sports performance, as it lowers exercise test duration under conditions of maximal exercising and increases the heart rate below maximal exercise levels.[239,404] Sports performance is also lowered by pot-induced rise in blood pressure as well as lowered psychomotor activity. It is difficult to correctly interpret urine samples of persons (i.e., athletes) for cannabis use because of the complex issues of prolonged cannabis excretion (*see above*).[404] The World Anti-Doping Agency has banned cannabis as a drug allowed by their athletes, and this plant has been on the list of prohibited drugs of the International Olympic Committee since 1989.[207,405,406]

Cannabis and MVAs

The deleterious effect of cannabis on driving ability with increase in motor vehicle accidents (MVAs) has been known for many decades.[311,407–411] Clinicians should know that adolescents and young adults driving after cannabis consumption (often complicated by alcohol use as well) leads to an increase of two-times or more of motor vehicle accidents (MVAs) with the possibility of injury and death.[1,242,243,311,412–424] Current research suggests that the precise psychomotor-induced impairment in driving ability under the influence of cannabis can vary in different persons and may be altered by one's protein kinase B (AKTI) genotype with effect on the inferior frontal cortex.[425]

Driving impairment is worse in infrequent cannabis users after smoking versus chronic users; habitual smokers maintain a THC level from tissue sequestration physiology.[116,117,126,134,135,426] Those who are occasional cannabis users may have an increased peak plasma THC level (21–267 μg/L) from smoking cannabis, leading to acute intoxication in contrast to a lower peak THC level (1.0–11.0 μg/L) in a habitual (daily) cannabis user.[427] Cannabinoids can be found in blood tests of chronic cannabis smokers even 1 month after stopping this drug; such findings have implications for persistent neurocognitive impairment in cannabis users as well as development of zero-tolerance versus low tolerance in cannabis use and driving laws.[428]

Consuming cannabis alone increased the risk for MVAs, which increases with higher amounts of cannabis taken because of impairment in psychomotor function, cognition, and driving execution.[1,412,417,428–430] The use of cannabis and alcohol increases risks of MVAs more than the use of cannabis alone.[419,424] Distortion of oncoming vehicle headlights can occur under the influence of cannabis, leading to MVAs. A study in California revealed that the rate of weekend drivers who tested positive for tetrahydrocannabinol (THC) was nearly 20% at night.[416]

Tests for cannabis typically used at MVA sites are not sensitive enough to detect THC, and urine tests for THC are not as accurate as plasma THC levels in assessing MVA risks (1,187).[1,426] Cannabis and alcohol are not the only drugs consumed by drivers in fatal crashes, as various drugs including prescription medications are increasingly found as well.[431–435] However, clinicians must teach their patients that cannabis has increasingly been found in fatally injured drivers over the past decade, as noted in a recent study in the United States from 1999 to 2010.[436] The use of synthetic cannabinoids is also associated with impaired driving similar to that seen with smoking "natural" cannabis.[437]

Clinicians should teach their patients not to drive under the influence of cannabis and that it leads to increased MVAs, especially with higher doses of THCs and with the addition of other illicit drugs. If the person has smoked pot and must drive, he/she should wait at least several hours, though a designated driver who has not smoked pot would be best.[419,420] Drivers should also know that cannabis consumption can increase road rage, and passengers should know that they should not be in a vehicle operated by a driver under the influence of pot.[421,422] Those under the influence of cannabis (and other drugs such as alcohol) should use public transportation, and public health officials should ensure that their communities have adequate public transportation.[423] Table 16 summarizes points that clinicians can make to their patients about smoking pot and MVAs.

Cannabis and psychiatric adverse effects

This section considers cannabis effects on the adolescent brain, links of cannabis smoking to psychosis, and the American Psychiatric Association's 2013 classification of Cannabis-Related Disorders.

Cannabis effects on adolescent brain development

Many studies have shown structural brain differences between adolescents who use marijuana compared with those who do not.[438–453] Such changes are especially significant in areas of the brain with a high density of cannabinoid receptors. Chronic use of marijuana by adolescents causes excessive stimulation of cannabinoid receptors, which has been shown to interfere with normal pruning of synapses during adolescence.[443] Chronic use of marijuana by adolescents also has been shown to be associated with asymmetrical increase in the size of hippocampi and amygdalae and enlargement of the cerebellum.[445] There is thinning of the frontal cortex in adolescent marijuana users.[446] Regular marijuana use at early age affects normal white matter development with impaired axonal connectivity.[438,439,444,447]

Studies in adolescents who used marijuana on a regular basis show a brain structure–functional correlation.[439–442] These include inattention, impulsivity, impaired executive function, memory loss, decreased coordination, distorted visuospatial perception, altered awareness of passage of time, decline in intelligence quotient (IQ), and impaired novel learning (Table 17). Animal and human studies suggest that the prevalence of cannabis abuse is increased in those with attention deficit/hyperactivity disorder (ADHD) versus that found in the general population, though the complexities of this relationship require more research.[454–458]

A report of 162 adolescents receiving inpatient treatment for problems related to drug dependence (including cannabis) noted ADHD in 34% of this group.[459] Males with ADHD and conduct disorder are at an increased risk to start substance use early—including cannabis.[460] Those with ADHD may use cannabis for self-medication, and research suggests that those with ADHD and substance use disorders may have lower striatal dopamine transporter density than those with ADHD and no comorbid substance use disorders.[461,462]

Thus, what the clinician should understand is that considerable animal and human research concludes that the developing brain, with its high neuronal plasticity, is vulnerable to exposure

Table 16
Clinician teaching to patients about cannabis and driving (see text).

(1) Cannabis smoking (including Spice drugs) increases risks for MVAs (double or more)
(2) Cannabis plus other drugs (i.e., alcohol) increase risks for MVAs even more
(3) If one has smoked pot, wait at least 8 h before driving a vehicle
(4) One should never be in a vehicle driven by one under the influence of pot
(5) Pot consumption increases road rage
(6) If one has smoked pot, take a bus or taxi home; do not drive!
(7) Communities should have adequate public transportation services so its citizens can get home safely if under the influence of cannabis

Table 17
Potential adverse CNS effects in adolescents smoking pot (see text).

Decline in IQ
Decreased coordination
Distorted visuospatial perception
Impaired executive function
Impaired novel learning
Impulsivity
Inattention
Memory loss
Neuropsychiatric disorders
Cannabis dependence
Others (see text)

to exogenous cannabinoids, particularly in the perinatal/prenatal period and during young adolescence.[438–453] Animal and human studies suggest that *early* onset of cannabis use (i.e., early adolescence) can increase risks for cognition dysfunction, CNS changes (i.e., low striatal dopamine release), neuropsychiatric disorders, cannabis dependence, and consumption of additional illicit drugs.[451,463] Cannabis use often develops in adolescence and early adulthood, which, as noted, is a vulnerable time for subsequent adverse brain effects.[464,465] Though more research is needed to understand the effects of cannabis on the developing brain, adolescence is a dangerous time to smoke cannabis.

Cannabis and psychosis

Multiple studies show an association between marijuana use and psychosis as well as an increased risk for schizophrenia.[438,439,441,466–470] Though this association is complex, research is beginning to unravel its secrets.[471] Increased rates of psychosis are seen with chronic use of cannabis, especially if the newer synthetic cannabis drugs are used.[466,472,473] The risk of psychosis is greater in adolescents who consume cannabis than in those who begin smoking marijuana in adulthood.[467] An earlier age of schizophrenia onset is noted in those who smoke cannabis as well as a reduction in gender difference in the age of onset.[474] Also, the course and prognosis of cannabis-induced schizophrenia may be worse than that found in those with schizophrenia who do not smoke cannabis.[475]

Regular cannabis use leads to a two-times risk for schizophrenia and psychotic symptomatology in part due to endocannabinoid system disturbance with disruption of normal signaling and functioning.[476] Persons with schizophrenia commonly consume cannabis, which can lead to paranoia in about 40% of those with this psychosis; smoking marijuana can lead to hospitalization at higher rates than those who do not use this drug.[477,478] Chronic cannabis consumption may change the central nervous system's structure and function in both adolescents and adults.[479] Persons with schizophrenia who smoke marijuana may develop cannabis dependence.[480]

Research has suggested that cannabis-induced schizophrenia may be caused by dysfunction of late postnatal maturation based on dysregulation of glutamatergic transmission that results in prefrontal neurocircuitry abnormalities.[481] As noted earlier, the developing adolescent brain is at risk for injury from cannabis; exposure of youth to marijuana during critical times in adolescence with certain doses may induce abnormalities of the prefrontal cortical neurocircuitry that may induce schizophrenia in susceptible youth.[481] It is not possible to predict which youth is susceptible to psychosis when smoking cannabis.[467]

A mean time of 7.0 $\pm$ 4.3 years has been reported between the onset of marijuana smoking and onset of psychosis.[466] Individuals at risk for the development of psychosis may be susceptible to cannabis-induced loss of brain volume involving the cerebellum, prefrontal cortex, and cingulate.[482] Other features of cannabis-induced psychosis include self-mutilation and the failure of improvement of psychotic symptoms with cannabis cessation.[483,484]

Fortunately, most cannabis smokers do not develop psychosis, and the development of psychosis in cannabis smokers seems to involve a complex interplay of molecular–genetic–environmental factors which includes anandamide and other biological constituents or influences.[470,472,485–488] Unfortunately, research notes a link between cannabis smoking and increased risk for suicide in those with psychosis and also those without psychosis.[489] Clinicians should teach their patients that cannabis smoking and schizophrenia development share various similarities such as reduced motivation, hallucinations, initiation in late adolescence, and neuropsychological deficits.[490]

This cannabis–psychosis link requires further research to uncover its etiology as this 21st century continues. Cannabis smoking is a very common illicit drug to use for those with psychosis and disruptive disorders.[491,492] Individuals with psychosis may smoke cannabis at higher rates than the general population as a means of combating negative aspects of schizophrenia (i.e., depression and boredom) with cannabis-induced euphoria.[493] However, positive effects on neurocognition were not identified in research on persons with schizophrenia who consumed cannabis.[494] Cannabis smoking can also prompt the onset of psychotic symptoms in persons thought to be otherwise healthy, and the induced paranoia and/or delusional thinking may occur due to THC effects on striatal and prefrontal function.[493]

What confuses this picture is that cannabis can have opposite effects on different smokers, and some research does not establish an association between cannabis smoking and symptoms of psychosis—especially with low or moderate cannabis use.[493,495] The phytocannabinoid cannabidiol (CBD) (Table 6) can have antipsychotic effects, and the presence of CBD may result in the absence of psychosis development in many cannabis smokers.[493,496] Research suggests a modulating effect of cannabidiol (versus THC) based on functional MRI of the brain.[497,498]

It seems that patients with schizophrenia smoking cannabis are particularly sensitive to cannabis-induced brain injury, though cannabidiol may provide a protective effect from loss of brain volume; however, there is not sufficient research to prove that there is an antipsychotic effect from cannabidiol.[490,499] In summary, clinicians must teach their patients that, based on much research (i.e., surveys, experimental studies, case studies, and epidemiological work), there is a link between the development of psychosis and cannabis smoking in some persons.[500]

Cannabis-related disorders

The American Psychiatric Association has identified a number of Cannabis-Related Disorders (Table 18).[501] Its 2013 Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5),[501] instituted a number of changes to the diagnostic criteria of all substance-related disorders (SRD) in general as well as for Cannabis use disorder (CUD) in particular. In the previous DSM-IV-TR[502] manual, SRD were classified into substance *use* disorders (SUD) and substance-*induced* disorders (SID). SUD were further classified into "abuse" and "dependence" disorders according to specific substances, as for instance, alcohol "abuse" and "dependence," opioid "abuse" and "dependence," and so forth.

SID included intoxication, withdrawal, delirium, and anxiety, as induced by specific substances. For example, this includes alcohol intoxication, alcohol withdrawal, and alcohol-induced delirium. The diagnoses of "abuse" and "dependence" categories required their own distinct criteria. Abuse could be diagnosed by meeting only one of those criteria, while dependence required at least three criteria to be met.

Table 18
2013 DSM-V cannabis-related disorders.[501]

Cannabis use disorder (mild, moderate, and severe)
Cannabis intoxication (with and without perceptual disturbances)
Cannabis withdrawal
Other cannabis-induced disorders
Unspecified cannabis-related disorders

DSM-5 kept the classification of SUD and SID. However, for SUD, it eliminated the previous diagnostic distinction between abuse and dependence and crafted the single category of "Substance Use Disorder," measured on a continuum from mild to severe. Thus, instead of treating abuse and dependence as separate, discrete entities, a concept with which many experts disagreed, DSM-5 became more aligned with clinicians' understanding that patients' conditions can vary along a severity continuum. Meeting the SUD 2–3 criteria indicates a mild disorder; 4–5 criteria, a moderate disorder; and 6 or more, a severe disorder.[501]

DSM-5 also introduced three additional general changes from its predecessor: (1) The diagnostic threshold was increased so that now at least two criteria (instead of one) are required to have an SUD. (2) A new criterion was added, "craving," defined as an intense desire or urge for the drug. (3) Finally, the "problems with law enforcement" criterion was eliminated[503] because of "cultural considerations that make the criteria difficult to apply internationally." DSM-5 also made a specific change to the diagnostic criteria for cannabis by adding a withdrawal syndrome, not previously included in past editions. The cannabis-related disorders most likely to be seen in a primary care practice are CUD and, to a lesser degree, intoxication and withdrawal. The reader can refer to DSM-5 for the most updated set of diagnostic criteria.[501]

Medical marijuana: Summary

This discussion has reviewed some of the research seeking to use cannabis for medical treatments and also reviewed some of the literature about potential medical, behavioral, and psychiatric adverse effects of cannabis smoking observed over the past half century and more. The limited approved indications for a few synthetic cannabinoids (dronabinol and nabilone in the United States) and the phytocannabinoid nabiximols (in Canada and other countries) has been considered. What should the clinician conclude about "Medical Marijuana," which is a hotly discussed topic in national- and state-level politics, the criminal justice system, and now in medicine across the board? As such, there are entanglements in the discussion of marijuana as medicine that need to be dissected out in order to clearly examine the issue of marijuana's medicinal legitimacy. There are actually three clear issues surrounding marijuana: decriminalization, legalization, and medicinal.

Cannabis decriminalization

The *decriminalization of marijuana* seems to be appealing to many interested parties, as it appears that many users of marijuana get into the criminal justice system when they are arrested. The arrest and subsequent disposition leads to a lifetime of difficulties thereafter in terms of opportunities for housing, governmental financial opportunities, and employment. There is a tremendous expense of taxpayer dollars for prosecution and incarceration of those convicted of crimes related to marijuana upwards from 9.5 billion dollars in 2002.[504] Some estimates of total cost are reported as high as 20 billion dollars annually. It has been suggested that when individuals are arrested, they should be accessed for a SUD and undergo treatment instead of incarceration. Treatment costs ($4,500 per year) less than incarceration ($27,000 per year), so the taxpayers save in this scenario.[505]

Cannabis legalization

The thought of the *legalization of marijuana* seems to promise many of the issues we see with the legalization of alcohol and tobacco in terms of youth use and abuse. There is a fear in the addiction treatment world that early experimentation and exposure will lead to more cases of substance use, abuse, and addiction. There are no safeguards that the legalization of marijuana will not lead to same problems we see today with alcohol, tobacco, and prescription drug among

adolescents and young adults. There are many non-scientific articles available about the pros and cons of legalization; however, scientific literature is lacking.

Medical use of cannabis

The *medical use of marijuana* has some promise in that it has been attributed to have medicinal properties since 200 AD. In the 19th century, Europe became very interested in the medicinal effects of marijuana. Irishman Dr. William O'Shaughnessy conducted clinical and non-clinical trials in India with cannabis extract preparations. Interest then spread to America and throughout Europe. Since that time, more research has been performed and more reports have been received regarding the medicinal properties of marijuana.[506] Some of this literature has been reviewed earlier in this article. This section seeks to bring these issues into better focus in terms of what is known scientifically and what needs to happen regarding the notion of marijuana as medicine.

Cannabis chemistry

As already noted, the marijuana plant has more than 460 psychoactive compounds. Of those 460 compounds, approximately 66 compounds are cannabinoid in structure. The active compound of *THC* predominates all of the compounds and has been identified as the compound with the most psychoactive property; THC has been identified and synthesized.[507]

Research performed in the 1980s and 1990s revealed that there are cannabinoid receptors distributed throughout the brain, CNS, peripheral nervous system, and other organ systems (the uterus and the testes) and of significant clinical potential significance, the immune system. These receptors are referred to as endocannabinoid receptors.[508] This discovery has lead to an increasing momentum to develop both agonist and antagonist medications that may be helpful in treating cannabis-related disorders or exert a medicinal effect attributed to currently smoked marijuana.

Most exciting is the identification of CB_1 and CB_2 receptors. The discovery and study of these receptors have lead to better understanding of the effects of cannabis and of how it affects chemical changes when smoked. These receptors can be studied more in depth and with the purpose to give rise to information that can be useful in the development of clinically useful medications.[509]

The isolation and synthesis of the compound *Cannabinol (CBD)* appears to be the best prospect and candidate for future industry research and development of a medication that can undergo FDA approval for clinical use.[510] CBD has very little psychoactivity; it empirically has been useful in treating young children with intractable seizures disorders. CBD may join other synthetic, FDA-approved, cannabis-based medications (dronabinol) available to treat yet-to-be-defined medical illnesses and conditions.

The clinical concerns of smoked marijuana

The political and legal concerns about smoked marijuana are well documented. The federal government has determined that it has no medical benefit, hence its classification as a Schedule I drug and its designation as an illegal substance. Some states have approved the use of smoked marijuana, by voting ballot or legislation for use to help alleviate some apparently intractable medical conditions. These issues are discussed elsewhere in this article and in the literature. This section will focus on the clinical concerns.

Purity of product and standardization of dose are significant clinical concerns. Traditionally, medications that are FDA approved meet these standards. Smoked marijuana lacks these controls. Batches of marijuana vary greatly, and the potency varies from one strain to another. The purity of product is also a concern, as some plants are contaminated by pesticides, fungus, and metals. There are no published standards for growing, cultivating, or distributing marijuana that is grown to be smoked.[506]

Without FDA approval and peer-reviewed clinical trials it is nearly impossible to prescribe any dosing. How can physicians instruct patients to smoke marijuana? What are the unit doses?

Physicians do not have guidance on dose or dosing frequency. How can physicians direct inhalations; deep or shallow? There are neither standard prescribing guidelines nor patient warnings or black box instructions that are all available with FDA-approved medications.

What are the legal liabilities that physicians face recommending smoked marijuana as medicine? In fact, physicians are merely "gatekeepers" as to who can be allowed to smoke marijuana without fear in states that have legislatively approved marijuana use as medicine. Physicians *do not prescribe; they certify* that persons meet legislatively established criteria to receive marijuana from a dispensary. Each state has varying regulations regarding marijuana as medicine. Where does physician responsibility and liability reside when non-FDA-approved treatment is implicit?

ASAM's recommendations regarding medical marijuana

The American Society of Addiction Medicine (ASAM)[506] researched volumes of literature published about marijuana and specifically marijuana as medicine and compiled an expert panel opinion in their "White Paper." Among discussions of the science, the ethics, and the law, recommendations for physicians were also developed. These recommendations are provided in Figure 1.

Conclusions and recommendations. Any serious discussion regarding marijuana has to be clearly articulated and defined, as the issues of decriminalization and legalization are often confounding the separate issue of marijuana as medicine. It is important that discussions, research, and policy making focus on evidence-based information that is readily available regarding marijuana as medicine. At this juncture, more information from clinical trials and research is needed.

Marijuana use as medication has been legislatively approved in a few states, but still regarded as a Schedule I substance by the federal government, indicating cannabis has no medicinal use and is illegal. To date, marijuana is the only substance that has been designated as medicine via legislation as opposed to approval through the FDA. There are two routes of approval available for marijuana: the standard medication approval route and the approval route for botanicals. Marijuana has not gone through either approval process.

Physicians who become involved in evaluating people for certification to use marijuana as medicine need to be fully aware of liability risks in recommending marijuana. Marijuana is not federally approved by the FDA, and therefore, information is lacking about product purity, standardization of dose, and other patient-safety and black box warning risks. This is truly a situation in which the risk–benefit ratio to the patient *and* the physician should be carefully weighed.

Identification and management of cannabis-related disorders in the primary care office

Introduction

Another aspect of what clinicians can do with regard to their patients using cannabis is to provide identification for and management of cannabis-related disorders. This discussion considers what the clinician can do in this regard in the primary care office. Indeed, this is an important task as noted by the high prevalence of cannabis smoking occurring in the world, as reviewed earlier. An even more worrisome finding is that about 25% of 19.8 million total users met the criteria for Cannabis Use Disorders (CUD).[82] A large percentage of afflicted individuals fail to seek treatment, which might reflect impairments in their recognition of the severity of the disorder. Some believe this is a purposefully volitional attitude but such "denial" might instead reflect brain dysfunction.[511]

At any rate, of the 7.6 million persons aged 12 years or older who needed treatment for an illicit drug use problem in 2013, only 1.5 million (19.5%) received it at a specialty facility. Of the remaining 6.1 million persons who needed but did not receive treatment, only 395,000 (6.4%)

1 *ASAM asserts that cannabis, cannabis-based medications, and cannabis delivery devices should be subject to the same standards that are applicable to other prescription medications and medical devices and that these medications or devices should not be distributed or otherwise provided to patients unless and until such medications or devices have received marketing approval from the Food and Drug Administration.*

2. ASAM recommends its members and other physician organizations and their members reject responsibility for providing access to cannabis and cannabis-based medications until such time that these materials receive marketing approval from the Food and Drug Administration.

3. ASAM rejects smoking as a means of drug delivery since it is not safe.

4. ASAM supports the need for federal regulatory standards for drug approval and distribution. ASAM recognizes that states can enact limitations that are more restrictive but rejects the concept that states could enact more permissive regulatory standards. ASAM discourages state interference in the federal medication approval process.

5. ASAM rejects a process whereby State and local ballot initiatives approve medicines because these initiatives are being decided by individuals not qualified to make such decisions (based upon a careful science-based review of safety and efficacy, standardization and formulation for dosing, or provide a means for a regulated, closed system of distribution for marijuana which is a CNS drug with abuse potential).

6. ASAM asserts that physician organizations operating in states where physicians are placed in the gate-keeping role have an obligation to help licensing authorities assure that physicians who choose to discuss the medical use of cannabis and cannabis-based products with patients:

- *Adhere to the established professional tenets of proper patient care, including*
  - *History and good faith examination of the patient;*
  - *Development of a treatment plan with objectives;*
  - *Provision of informed consent, including discussion of risks, side effects, and potential benefits;***
  - *Periodic review of the treatment's efficacy;*
  - *Consultation, as necessary; and*
  - *Proper record keeping that supports the decision to recommend the use of cannabis*
- *Have a **bona fide** physician-patient relationship with the patient, i.e., should have a pre-existing and ongoing relationship with the patient as a treating physician;*
- *Ensure that the issuance of "recommendations" is not a disproportionately large (or even exclusive) aspect of their practice;*
- *Not issue a recommendation unless the physician has adequate information regarding the composition and dose of the cannabis product;*
- *Have adequate training in identifying substance abuse and addiction*[506]

**** If a physician recommends the use of cannabis for a minor, parents and/or legal guardians must be fully informed of the potential risks and benefits of such use and must consent to that use.**

Fig. 1. Recommendations of the American Society of Addiction Medicine (ASAM) regarding Medical Marijuana[506]*, *Used with permission from American Society of Addiction Medicine.

reported that they perceived a *need* for treatment. While about one-third of these individuals stated not being ready to stop as the reason for not seeking treatment, the largest percentage offered reasons that could have been possibly resolved by education, correction of misperceptions, or referral to charity care/federally funded treatment sites.[82]

Therefore, primary care physicians (PCPs) have the opportunity to play a significant role in reducing marijuana harm by addressing these issues and recommending certain interventions during routine visits for the increasing number of Americans who develop CUD. This section describes a program that can be used by PCPs in their offices termed *Screening, Brief Intervention, and Referral to Treatment (SBIRT)*,[512] which has been shown to lower alcohol and other substance use. The program's ample organizational support, documented clinical success, training availability, ease of implementation, and third-party reimbursement options make it a first choice for physicians wishing to have an in-office impact on decreasing cannabis use among their patients. Other available behavioral and pharmacological options are also reviewed to familiarize clinicians with the care approaches patients receive when the severity of the condition requires referral to specialists.

The rapidly changing marijuana regulatory environment

Most substances with potential for *abuse*, excluding those FDA approved for medical use, have been illegal for anyone to purchase and consume. Adults, however, are legally permitted to purchase some addictive substances that can result in great self-harm, even when used as intended. Examples of these are tobacco and alcohol and more recently, in some states, marijuana. There are no rules restricting the private use of these products in any desired amounts unless individuals consume them in certain forbidden locations, interfere with societal peace, or violate transportation laws. There are also legal substances such as opioid medications that become illegal when obtained and abused as a result of diversion. There is no question that substances of abuse, whether legally available or illicit, can cause great harm.

Over the years, however, society has struggled with how to best utilize *legal status* as a tool to decrease and hopefully eradicate such harm. Legal status is not an inherent property of a substance but a geopolitical attribute, conferred to it by society. What is legal today, particularly as it pertains to substances, can be illegal tomorrow. For instance, the US 1920s prohibition period saw a pendulum swing in the societal mores as alcohol went from legal to illegal and back to legal status all within the span of a few years.[513]

Although the question of whether a substance is legal or illegal is undoubtedly of great importance to society in general, it has up to now been of greater relevance to lawyers than to physicians. Physicians assist patients with the medical sequelae of abuse regardless of the legality of the substance in question and are not legal enforcers. Determining what the legal status of a substance shall be is not the task of the medical profession, but that of the democratic process that guides a government's decision on the matter. Although medical organizations can provide the government with expert opinions, physicians understand that their role is first to *do no harm* (*primum non nocere*) and then apply their medical skills and compassion to help those with medical problems. Substance-related disorders are such type of conditions and have significant morbidity and mortality.[1,57,493] PCPs and specialists such as addiction physicians recommend scientifically validated therapies with the potential to bring great relief to those affected by substance-related disorders.

There is considerable antagonism between proponents and opponents of drug legalization. It is beyond the scope of this discussion to review the merits and/or concerns regarding legalization status (*see below*), but an excellent article is available on the subject elsewhere.[514] Physicians, as private individual citizens, can contribute to this process by recommending their views to representatives in Congress. At any rate, marijuana is rapidly becoming legalized in the US and the world and with more states as well as countries permitting its recreational use without penalties under certain circumstances.

While this change would not be of significant consequence to the usual practice of medicine, it could have public health implications in that evidence may already suggest an increase in use and unintended harm in regions where marijuana has been legalized.[515] The suggestion that legalization can result in harm is often opposed, particularly in the public media.[516] However, if wider opioid availability was at least in part responsible for the opioid prescription dependence epidemic,[517] increased marijuana availability may lead to more frequent cannabis disorders as well. To date, however, this logical assumption has not been confirmed by public health research.

While the legal versus illegal status of marijuana does not impact the usual practice of medicine, the concept of "medical" marijuana, however, does present operational challenges for physicians. Validated scientific research methods are used to determine whether an agent is safe and effective and can be recommended to the population at large for therapeutic purposes. When an agent successfully undergoes this methodology, the US Food and Drug Administration (FDA) approves it for commercialization. Historically, marijuana has been used for ages to informally treat ailments[493] but was passed up for medical research because of its intoxicating effects. It was also classified as a Schedule I substance under the Controlled Substances Act. Schedule I substances are considered to have a high potential for dependency and no accepted medical use, making distribution of marijuana a federal offense.[518]

Due to advances in the understanding of the endocannabinoid system, there has been renewed interest in some of the naturally occurring as well as synthetic cannabinoid molecules, and many scientific studies are underway to determine their therapeutic potential (*see above*). The marijuana *plant*, however, entered the therapeutic realm via an unusual path. The conclusion that the plant possessed medical properties by smoking or ingesting departed from FDA guidelines. As of this writing, marijuana can be medically "recommended" in 23 US states[519] as a result of legislative rather than scientific efforts.

Physicians are by nature innovators. They have been instrumental in the development of amazing therapies, advocating for their patients' health even when some of these therapies began in controversy. Physicians do encourage pharmacological research, and it would be hard to find one against investigating the therapeutic properties of cannabinoid compounds, those either naturally available or newly built as result of technical advances. However, many physicians are troubled by the unclear regulatory environment of medical marijuana and, moreover, by the assertion that *smoking* marijuana is medicinal when, as review previously, scant scientific proof exists (*see above*).[520]

There are several other issues of concern. First, no physician would want to repeat the type of mistake made in the last century, when poor access to medical evidence resulted in physicians allowing tobacco ads in the most prestigious medical journals, with advertisements implying some cigarette brands had medicinal properties.[521] Along these lines, it is worrisome that the burgeoning marijuana industry is already following the same successful business strategy utilized by tobacco in the 20th century, such as increasing potency of the drug and creating new delivery devices.[52]

Furthermore, is it reasonable for physicians to recommend a delivery system that is the leading cause of home fire deaths?[522] Finally, how are physicians supposed to navigate the legal pitfalls of recommending a substance deemed illegal by the US Federal Government?[523] As reviewed in the publications referenced in this monograph, ample debate is being conducted in the literature regarding this topic.[523] In addition, other authoritative sources' evidence regarding the potential for marijuana harm[524] can assist physicians in determining their role regarding medicinal marijuana until further, wider, scientific research is available.

Identification and management in the primary care setting

As noted, PCPs are uniquely positioned to identify individuals at risk for SRD and can have significant impact on reducing the progression and morbidity of these conditions. For instance, research studies since the late 1970s have showed that structured screening and brief intervention efforts can improve treatment outcomes. An early study found that general

practitioners' (GP) advice to stop smoking, enhanced by providing an information leaflet and follow-up, had higher rates of smoking cessation than controls.[525] A later study concluded that a brief intervention by GPs with support and backup from a smokers' clinic can, when sustained on a continuous basis, reach sufficient numbers of smokers to reduce the prevalence of smoking in their practice populations.[526]

These findings supported the development of new approaches by the World Health Organization (WHO). In 1980, the WHO stressed the need to create efficient methods to detect individuals with harmful alcohol consumption at earlier stages to decrease the potential for sequelae and called for the development of strategies that could be applied in primary health care settings with minimal time and resources.[527]

Along these lines, the World Health Organization (WHO) sponsored a study to assess the relative effects of simple advice and brief counseling with heavy drinkers identified in primary care and other health settings in eight countries.[528] The study concluded that brief interventions were consistently robust across health care settings and sociocultural groups and could make a significant contribution to the secondary prevention of alcohol-related problems if adopted in primary care.[528] These approaches, which initially focused on addressing alcohol and tobacco disorders, were later expanded to all substances.[512]

In addition to the WHO, the US Institute of Medicine[529] and the US Substance Abuse and Mental Health Services Administration (SAMHSA) also recommended these structured principles. Eventually, the collaborative effort of all these agencies resulted in the creation of the SBIRT program.[530] This comprehensive, integrated, public health approach to the delivery of early intervention and treatment services for persons with substance use disorders, as well as those who are at risk of developing these disorders, is geared toward application in primary care settings.

Since 2003, the SAMHSA has been very active in recommending SBIRT and established a grantee program to implement it in primary care and community health settings for adults with substance use. The SAMHSA has fully or partially funded four portfolios: (1) SBIRT Cooperative Agreements to Single State Authorities (SSAs) for Substance Abuse Services, (2) SBIRT implementation on college campuses, (3) a pilot project for SBIRT implementation within Federally Qualified Health Centers, and (4) SBIRT implementation within medical residency programs.[531]

According to the SAMHSA's research, SBIRT results in short-term health improvements and possibly long-term benefits.[531] A study found that, in some instances, a brief motivational intervention appeared to facilitate abstinence from heroin and cocaine use at a 6-month follow-up interview, even in the absence of specialty addiction treatment.[531] Furthermore, data from the SAMHSA grant programs helped demonstrate the impact of SBIRT on patient health through documented reduction in alcohol and drug use 6 months after receiving intervention, improvement in quality-of-life measures, and reduction in risky behaviors. SBIRT also reduced the time and resources needed to treat conditions caused or worsened by substance use. For example, participants in the Washington State Screening, Brief Intervention, and Referral to Treatment (WASBIRT) program experienced a reduction in total Medicaid costs ranging from $185 to $192 per month.[531]

SBIRT consists of (a) *Screening* to quickly assesses the severity of substance use and identify the appropriate level of treatment, (b) *Brief intervention* that focuses on increasing insight and awareness regarding substance use and motivation toward behavioral change, and (c) *Referral to treatment* that provides those identified as needing more extensive treatment with access to specialty care.

How to SBIRT: A basic implementation guide for the primary care office

There is no question that, statistically, a number of patients under the care of PCPs are either contemplating using marijuana, already are using it recreationally, or are heavy users. This is also true for alcohol, tobacco, and many other addictive substances.[1,57,493] PCPs can take an active

role in routinely screening for such use with the goal of stopping the progression to a substance disorder or, when this is not possible, to make appropriate specialty referrals for further care. While this article focuses on marijuana, the SBIRT model is applicable to all substance-related disorders.

Therefore, this section SBIRT "how to" guide has wide applications that extend beyond cannabis. It is important to note that identification of risk and diagnostic evaluations are different medical procedures. SBIRT screens for individuals at risk and although those identified as high risk are very likely to have a condition, a definite diagnosis can only be made by physicians familiar with the diagnostic criteria and the field of SUD. These components are now reviewed: (a) *How to screen*, (b) *How to intervene briefly*, (c) *How to refer to treatment*, and (d) *How to get paid*.

a—How to screen

The main goal of screening is to determine a patient's level of risk regarding the use of substances within a range of *mild*, *moderate*, or *high* risk.[532] It is recommended that all patients aged 12 years and older be screened. The patient's level of risk, assessed by screening, will guide the physician's treatment recommendations. The first step in this process is to ask patients for permission to be screened. This should be introduced in plain language such as noted in Figure 2.

PCPs can tailor their own introductory explanation to their patient populations. The language suggested here in Figure 2 anchors on two important points: it clarifies that obtaining information on drug use is just one more set of data needed to improve care while it also reviews with the patient that sensitive facts will be kept confidential. Concerns about private information may be a barrier patients need to overcome in order to share problems with PCPs. Thus, before implementing SBIRT, physicians would want to institute robust processes for insuring the confidential safekeeping of records. The suggested language here also asks about substances "*that you may be using as medication*" to address not only opioid overuse but also marijuana that patients could be using medically.

Once permission for screening is obtained, the process need not involve the PCP's time directly and can be delegated to nursing or other ancillary professionals in the office. The actual screening, i.e., the *process of asking questions*, can be done by having a dialog with the patients directly, having them complete a form available in traditional paper-and-pencil formats, or completing a web-based form on a computer. Such forms, known as "screening tools," are well-researched rating scales with reliable psychometric properties.[531]

Although many such tools are available, in order to guarantee third-party reimbursement for services rendered, it is important that the office use a "validated" tool. One of the best tools is the US National Institute on Drug Abuse (NIDA)-modified ASSIST (NM-ASSIST)[533] that has a number of advantages as outlined in Table 19. This tool can be used for patients aged 18 years and older. For younger patients, the American Psychiatric Association has developed tools for youth 11–17 years old.[534] Pediatricians can thus follow the SBIRT model. A comprehensive review of their role is available elsewhere.[535] The NM-ASSIST is used as reviewed in Figure 3.[532]

b—How to intervene briefly

The level of SI risk will guide the PCP's intervention as follows.

> *"If it's OK with you I'd like to ask you some questions that will help me provide you with better medical care. You already know that this office is very interested in learning as much about your health as possible and you are the best source of information about yourself. Some of the questions I have asked you before involved information you would not share with anyone other than your doctor. This set of questions is on alcohol, cigarettes, and other substances with potential for addiction including some that you may be using as medication and others that may be illegal. I want to reassure you that I take your privacy very seriously and all the information that you provide will be only used for medical care, is confidential, and will be kept secure."*

Fig. 2. SBIRT initial screening language.

Table 19
Advantages of US National Institute on Drug Abuse (NIDA)-modified ASSIST (NM-ASSIST).[533]

Is validated
In the public domain
Takes a few minutes to complete
Comes in a quick screen form version (a prescreen) and a full-screen version
Has widely available free web-based training on how to use
Sponsored by a US government organization

Low risk. For low-risk[532] patients, the PCP can consider having a discussion about acceptable levels of use and the potential for future problems. For example, if the patient scored low just on marijuana, the PCP may state: *"It seems that you have experimented with using marijuana but fortunately this has not harmed your health yet. You may not know that marijuana can…(enumerate health risk, myths, etc.) As your physician, I encourage you to stop its use and avoid using other substances."*

This discussion shall be documented in the medical record. It is hoped that the brief intervention will reduce the progression of use. The PCP may follow-up in 3 months to assess the intervention's outcome and determine if further action is needed. If the patient, although scoring low levels, has acknowledged multiple substances and/or is on a high-risk category such as pregnancy, adolescence, or comorbid psychiatric problems, a more comprehensive intervention may be required.

Moderate risk. For moderate-risk[532] patients, the PCP can start a discussion by saying "Based on the screening results, you are at moderate risk of having or developing a substance use disorder. It is medically in your best interest to change your use of marijuana." A conversation can then be started regarding the patient's readiness to quit as well as assessing motivation and insight. For example, "Given what we've talked about, do you want to change your drug use?"

If the patient is unwilling to quit, the PCP can raise awareness about drugs as a health problem and state that it would be important to revisit the issue at future visits. If the patient is hopefully ready to quit, it would be appropriate for the PCP to initiate office-based interventions. These may include writing together a "change plan" that outlines the steps the patient will take to quit or reduce substance consumption (Table 20). The patient will take a copy of this plan home, and progress will be reviewed at the patient's next visit, which should be scheduled

1- PCP introduces self to patient and establishes rapport.

2- PCP (or delegated office staff) asks patients about past year drug use using the NIDA Quick Screen. If the patient answers "Never" for all drugs in the "Quick Screen", abstinence is reinforced. For example, PCP may say "It is really good to hear you aren't using drugs. That is a very smart health choice." *Screening is now complete*.

3- If the patient, however, screens positive on the Quick Screen, PCP proceeds to the full NM-ASSIST tool which has 8 questions that inquire about lifetime use, past 3 months use, and seeks information about symptoms consistent with a substance disorder such as "how often has your use of (first drug, second drug, etc.) led to health, social, legal or financial problems?" etc.

4- PCP determines the patient's risk level by scoring the form, as per instructions detailed on the tool, to obtain a Substance Involvement (SI) score for each substance. An SI score of 0-3 indicates "low risk," 4-26 "moderate risk," and over 27 "high risk." The patient will receive an SI score for each substance endorsed, not a cumulative score. Therefore, the patient's risk level may differ from drug to drug.

5- PCP reviews the screening results with the patient giving an opportunity to correct any mistakes and expand on any information. Based on the screening information, the PCP provides the most appropriate intervention, as described in the next section.

Fig. 3. Guide on how to use the US National Institute on Drug Abuse (NIDA)-modified ASSIST (NM-ASSIST).[532]

within 1 or 2 weeks. For patients who are able to follow the plan and make changes, the PCP can reinforce efforts and encourage additional goal-setting in subsequent visits. Patients who are not able to change and/or whose condition worsens will be considered high risk.

High risk. For high-risk[532] patients, a strong recommendation to change substance use is essential. The PCP shall consider making a statement such as:

"Based on the screening results, you are at high risk of having or developing a substance use disorder. It is medically in your best interest to stop your use of marijuana. I am concerned that if you do not make a change quickly, the consequences to your health and well-being may be serious."

A high-risk score on the NM-ASSIST tool suggests that further care will be necessary and that the patient would be best served by a referral to a specialist. Of course, whether to attend treatment or not will be the patient's decision. Follow-up appointments in these cases should be offered on a weekly basis during which the PCP would continue to accompany the patient in this process, remain involved in the medical care, and encourage change and pursuit of specialized care if this has not taken place.

Such encouragement is best delivered by utilizing a *Motivational Interview* (MI) approach[536] that upholds four principles: expressing empathy and avoiding arguing, developing discrepancy (increase awareness of the difference between where patients are and where they want to be), rolling with resistance (use it to advance rather than obstruct), and supporting self-efficacy (patients' belief that they can successfully make a change). A comprehensive review of MI is available elsewhere.[537]

c—How to refer to treatment

Once the PCP explains that, due to the high risks reported, specialized care in conjunction with medical follow-up is recommended, a referral can proceed. Most PCP offices have developed relationships with psychiatrists and other addiction specialists they trust and prefer to whom they refer their patients. The multitude of insurance plan networks or lack of insurance, however, mandates that PCPs be familiar with additional local care options. Fortunately, the SAMHSA has developed an excellent web tool to facilitate locating appropriate specialists[538] where PCPs can enter their location and obtain a list of local hospitals, clinics, and other substance abuse service providers.

d—How to get paid

Because of the importance of identifying substance abuse early in its course and the significant role that PCPs can have in harm reduction, professional organizations successfully advocated for reimbursement of these activities. As a result, PCPs can bill utilizing CPT codes for services that cover all aspects of SBIRT. A comprehensive guide to coding can be found on the SAMHSA web page.[539] This guide reviews Medicare, Medicaid, and commercial insurance guidelines to obtain reimbursement as well as provides brief vignettes that serve as models for chart documentation.

Table 20
Steps of a "Change Plan" for patients seeking to quit cannabis

Enumerate
(1) The reasons why the patient wants to change
(2) Whose help the patient will seek and in what way their support network can help
(3) What problems can be anticipated in achieving the goal
(4) What specific recommendations the PCP has made such as self-help groups or medication

Specialized treatment approaches

As discussed in the section How to refer to treatment, if SBIRT shows that a patient is at high risk or the CUD progresses despite in-office interventions, it is recommended that patients receive more intensive specialized treatment not usually available in primary care office settings. Such treatment includes behavioral and pharmacological approaches that will be described in the following sections.

Behavioral treatment

Many different types of therapies (Table 21) have been used, but the most studied are Motivational Enhancement Therapy (MET), Cognitive-Behavioral Therapy (CBT), and Contingency Management (CM), in individual and group formats. In addition, family therapy, in particular for adolescents, has also shown effectiveness. While these therapies are not CUD specific, their effectiveness to treat other SUDs has been widely documented. Results in CUD are positive, but controlled research is less abundant.

Motivational Enhancement Therapy (MET) stresses a non-confrontational approach that builds on patients' motivation and commitment for change. It seeks to help patients resolve ambivalence about change, reinforces statements about why they want to change, and strengthens their commitment to actually change their substance use behavior. It shares elements of *Motivational Interview* (MI) but it is of longer duration.[540]

Cognitive- Behavioral Therapy (CBT) focuses on teaching patients skills relevant to quitting marijuana and avoiding or managing other problems that may interfere with good outcomes. Patients learn functional analysis of marijuana use and cravings, self-management planning to avoid or cope with drug use triggers, drug refusal skills, problem-solving skills, and lifestyle management.[541] Ultimately, the goal of CBT is to have the patient acquire skills to cope with life stressors and high-risk situations in more adaptive ways than relapsing into previous cannabis use.

Contingency Management (CM) is the most behaviorist of the three approaches in that it considers abstinence behavior as an operant that is susceptible to reinforcement. This model asserts that the probability of abstinence increases when abstinent behavior is reinforced. In other words, patients earn money or prizes if they demonstrate completion of certain elements of treatment or remain abstinent.[542]

Multidimensional Family Therapy (MDFT) is a family-based outpatient treatment program for adolescent problem behavior, targeting major domains in the life of an adolescent.[543] The life domains include the youth, parents, family, friends and peers, school and work, and leisure time. MDFT views family functioning as instrumental in creating new, developmentally adaptive lifestyle alternatives for adolescents.

Research shows that behavioral therapy is effective for CUD, although long-term benefits have been difficult to achieve. There is also evidence that a combination of more than one behavioral approach increases effectiveness. For instance, a large controlled trial of treatment for marijuana-dependent adults, the Marijuana Treatment Project, followed up 450 dependent men and women in three sites comparing MET to a combination of MET and CBT to a placebo condition.[544] While the combination was superior, even with it, only 22.7% of subjects remained abstinent at 4 months, a percentage that declined to 15.3% at 9 months.

Table 21
Key behavioral therapies for substance use disorders

(1) Motivational enhancement therapy (MET)
(2) Cognitive-behavioral therapy (CBT)
(3) Contingency management (CM)
(4) Multidimensional family therapy (MDFT)

Many studies comparing combination approaches also show its superiority, but abstinence rates at 12 months remain under 37%. Other studies have not been able to prove that differences exist between active treatments, as all achieve similar and low abstinence rates compared to placebo.[545] Since there are many treatment methods available but great cost variability exists due to differences in length (single versus multiple sessions), format (individual versus group), and location (in person versus via internet), researchers are interested in confirming which options are the most resource effective.

A 2014 meta-analysis pooled the only 10 randomized controlled CUD studies available to date comparing various behavioral treatments against placebo conditions.[546] It concluded that the average patient receiving a behavioral intervention fared better than 66% of those in the control conditions. On the other hand, no differences were found between the effect sizes of the various treatments considered.

Therefore, the more cost-effective treatment dissemination strategies (e.g., group treatment or web-/telephone-based delivery) have the potential to be as efficacious for this population as individual, in-person treatment strategies. The consistent but low long-term improvement rates achieved with behavioral therapies have fostered a desire to search for more effective treatments with a special focus on pharmacological agents.

Pharmacological treatment for cannabis-related disorders

At the present time, no FDA-approved agents exist for the treatment of cannabis-related disorders. Behavioral treatment, despite its limitations, remains the treatment of choice for CUD. Several agents, however, have been used off-label and others have been investigated or are in the process of undergoing clinical trials (Table 22). In order to better understand the potential for pharmacological interventions, it is important to understand the cannabinoid system that has been considered earlier in this monograph.

The biological effects of marijuana and Δ9-tetrahydrocannabinol (THC) (Table 7), its major psychoactive component, are mediated by two G protein-coupled cannabinoid receptors known as CB_1 and CB_2.[145] CB_1 receptors are found mainly at the terminals of central and peripheral neurons, where they inhibit the release of a number of different excitatory and inhibitory neurotransmitters. The distribution of these receptors within the central nervous system coincides with areas involved in processing cognition and memory, motor function, and analgesia.

CB2 receptors, on the other hand, are located predominantly in immune cells and modulate immune cell migration and cytokine release both outside and within the brain. THC is an "exogenous" cannabinoid, and it produces euphoria from effects on cannabinoid receptors in mesocortical and limbic systems.[547]

Table 22
Pharmacologic agents studied for cannabis-related disorders (see text).

N-arachidonoylethanolamine (anandamide)
2-Arachidonoyl glycerol (2-AG)
Dronabinol
Nabilone
Cannabidiol
Benzodiazepines
Antipsychotics
Lithium
Nefazodone
Alpha 2 adrenergic agonists
Lofexidine
Nabiximols
Gabapentin
N-acetylcysteine (NAC)
Others (see text)

Interest in cannabinoid receptors led to the identification of "endogenous" cannabinoids, synthesized by the body, which bind to CB_1 and CB_2. The most well known are N-arachidonoylethanolamine (anandamide) and 2-arachidonoyl glycerol (2-AG) (Table 6). The endocannabinoid system consists of these two compounds, additional ones found more recently, and the CB_1/CB_2 receptors.

No cannabinoids have been approved for the treatment of *cannabis* disorders. On the other hand, because the endocannabinoid system has an impact on many different functions, and because over history, marijuana has been used empirically to treat various ailments, some cannabinoids have been FDA approved for indications other than cannabis disorders. A major limitation is that these agents can have significant psychiatric adverse effects. Nonetheless, because of their FDA approval, some of these medications have been tried off-label for marijuana-related disorders.

For instance and as noted earlier, nabilone is a synthetic compound structurally similar to THC and is FDA approved as a controlled substance (CII) to treat nausea and vomiting associated with cancer chemotherapy (Table 8).[548] Dronabinol is a synthetic THC that was FDA approved as a controlled substance (CIII) for nausea resulting from chemotherapy and also to manage the loss of appetite in people with acquired immunodeficiency syndrome (AIDS) (Table 8).[549] Interest in non-psychoactive marijuana compounds led to studying cannabidiol, which is one of the naturally occurring substances.

As noted previously, cannabidiol has no psychotropic activity and, although it has very low affinity for both CB_1 and CB_2 receptors, it has been recently reported to act with unexpectedly high potency *in vitro* as an antagonist of CB_1 receptors in the mouse vas deferens and brain tissues.[550] Nabiximols is an agent that contains THC and cannabidiol at a 1:1 ratio and has been approved in Europe for multiple sclerosis spasticity (Table 7).[551] Not yet approved in the US, it is undergoing phase III trials for cancer pain only. The CB_1 receptor antagonist rimonabant entered the European mass market on the back of several trials showing weight loss benefits alongside improvements in numerous other elements of the metabolic syndrome. However, the drug was quickly withdrawn due to the emergence of significant side effects, notably severe mood disorders.[552]

Cannabis intoxication (CI)

The clinical picture of CI, except for a few cases, is usually mild, self-limiting, and does not require treatment. It is thus unusual for patients to present to the primary care office with CI. In instances of severe symptoms, patients visit the Emergency Room. Of concern is that between 2004 and 2011, marijuana-related emergency visits increased by 62% (*see below*).[553] Some preliminary data suggest an association between marijuana legalization/medicalization and increased emergency visits, at least as it pertains to pediatric patients.[554] More severe CI cases can result in high anxiety or psychosis, for which usual pharmacological treatment for these conditions such as benzodiazepines or antipsychotics may be indicated. A comprehensive review of the pharmacological treatments that have been tried in CI is available elsewhere.[555]

Cannabis withdrawal (CW)

Until the publication of DSM-5, CW had not been formally included in the American Psychiatric Association manuals, although the syndrome had long been observed by clinicians.[556] Unlike withdrawal from some other substances, while uncomfortable for the individual, CW does not result in severe health problems.[557] Nonetheless, CW was the subject of therapeutic interest, as there is some indication that it may predict cannabis relapse.[558,559]

Mirroring the treatment of other withdrawal states, researchers investigated the use of agonist substitution to mitigate withdrawal symptoms. For example, nabilone[560] and dronabinol[561] both showed a reduction in CW. Other non-cannabinoid psychotropics such as the mood stabilizer lithium and the antidepressant nefazodone have also shown to ameliorate symptoms.[562] Alpha 2 adrenergic agonists have been used successfully for opioid withdrawal. Lofexidine, one such older compound approved in Europe that has not gained FDA status yet, improved CW and was even more effective when used in combination with THC.[561]

Cannabis use disorders (CUD)

Psychotherapy of SUD (CUD included) has produced poor long-term results. For this reason, there has been interest in developing pharmacological options that could optimize outcomes. Researchers have studied several strategies. For instance, in an approach similar to the one used in Opioid Use Disorders, studies have focused on agents that modulate the cannabinoid receptors.

Synthetic agonists have shown mixed results. Dronabinol[563] failed to reduce cannabis use, but since nabilone showed some promise,[560] a pilot study is in progress to assess change from baseline in cannabis use at 10 weeks.[564] While dronabinol alone was not effective, its combination with lofexidine[561] decreased marijuana relapse in the laboratory. A larger phase III study that plans to enroll 180 patients is currently underway seeking to confirm the beneficial effects of this combination.[565]

Regarding endocannabinoids, a study currently underway is evaluating the therapeutic potential of augmenting anandamide by inhibiting the enzymes that cause its destruction.[566] Finally, the use of the naturally occurring cannabidiol was studied using the nabiximols formulation,[567] although this failed to reduce cannabis use. Cannabidiol alone, however, is also currently being investigated for cannabis cessation, although results are not yet available.[568]

A variety of other psychotropics such as antidepressants (escitalopram, mirtazapine, buspirone, fluoxetine, and venlafaxine), antipsychotics (quetiapine), and GABAb agonist baclofen have been tried with little success.[562] On the other hand, two agents gabapentin and N-acetylcysteine (NAC) have shown significant promise.

Gabapentin, an anticonvulsant, is a calcium channel/GABA-modulating agent. A 12-week, randomized, double-blind, placebo-controlled clinical trial was conducted in outpatients aged 18–65 years, who were diagnosed with current cannabis dependence.[569] Subjects received either gabapentin or placebo. Counseling was provided weekly to all participants. Cannabis use was measured by weekly urine toxicology and by self-report. Relative to placebo, gabapentin significantly reduced cannabis use as measured both by urine toxicology and self-report. In order to further confirm these findings, a larger study, planning to enroll 150 patients, is currently being conducted.[570]

NAC, an *N*-acetyl prodrug of the naturally occurring amino acid cysteine, has been proposed to modulate the glutamate system.[571] Glutamatergic transmission changes in the limbic reward circuitry[572] are linked to persistent drug addiction. In an 8-week, double-blind, randomized, placebo-controlled trial, treatment-seeking cannabis-dependent adolescents received NAC or placebo twice daily, as well as a contingency management intervention and brief weekly cessation counseling.[573] Participants receiving NAC had more than twice the odds, compared with those receiving placebo, of having negative urine cannabinoid test results during treatment. NAC was well tolerated, with minimal adverse events.

Findings supported NAC as a pharmacotherapy to complement psychosocial treatment for cannabis dependence in adolescents. In order to test the efficacy in adults, the National Institute on Drug Abuse Clinical Trials Network is currently conducting a study in patients aged 18–50 years.[574] Approximately 300 treatment-seeking cannabis-dependent adults will be randomized to NAC or placebo across six study sites in the US. The primary objective of this 12-week study is to evaluate the efficacy of twice-daily orally administered NAC versus matched placebo, added to contingency management, on cannabis abstinence. A significant advantage of NAC is that it is widely available as an over-the-counter supplement.

Acute THC-induced psychosis/delirium

This condition is becoming an increasing problem for clinicians in emergency medicine departments and also for Poison Control clinicians who are being called about its management. When the clinician encounters this patient s/he typically starts with management as with other induced psychosis and if agitation is not severe—provide a supportive environment with low

stimuli to help calm the patient, provide a benzodiazepine, and hope that the substance will be readily metabolized out of the patient. If these measures are not successful and the psychosis continues, the use of neuroleptics is the next step in management.

Unfortunately traditional psychotropic agents (i.e., haloperidol, olanzapine, thorazine, others) often are not beneficial for the patient who has developed acute, severe THC-induced psychosis/delirium. Though there is minimal research support, the severity of some situations has led some clinicians to use the powerful sedative, dexmedetomidine with or without benzodiazepine. This latter drug is an agonist of α_2-adrenergic receptors in the brain, is the S-enantiomer of medetomidine, is ten times more selective than clonidine, and can reduce benzodiazepine requirements in drug toxicity management.

This chemical with a central sympatholytic effect has been used by anesthesiologists in patients undergoing procedures including adults in intensive care units and has been FDA-approved for short term (< 24 h) sedation of adults during mechanical ventilation. It does not have the risk of respiratory depression seen with high doses of benzodiazepines. There has been some experience by experts with dexmedetomidine in pediatric patients. Peripheral α_2-receptor stimulation can led to bradycardia and hypotension. The role of this drug for acute, severe psychosis/delirium is under consideration as a way of reversing or counteracting cardiovascular and central nervous system overstimulation from drug toxicity. More cases induced by THC can be expected in a pro-cannabis society with an ever-increasing legalization mindset.

Conclusions

As discussed previously, marijuana is the most frequent illicit drug used in the United States. Elsewhere in this issue and in other recent publications,[524] experts warn of the significant morbidity resulting from CUD with limited treatment options that are currently available.[575,576] Proponents of legalization and medicalization of marijuana claim that research does not support a correlation between passage of these regulations and increased use.[577,578] It is possible, however, that not enough time has elapsed since passage for a link to be demonstrated, a possibility that even the article's authors consider.[562]

Clinicians should inform their patients that there are many known potential adverse effects from smoking marijuana that have been identified in the scientific literature of the past half century and more.[57] Because of the presence of these known potential adverse effects and the lack of scientific evidence supporting cannabis smoking as "medicinal," the US Food and Drug Administration, US Drug Enforcement Agency, and leading medical organizations have not approved of nor recommended marijuana smoking as treatment for medical or psychiatric disorders. The use of recreational marijuana should also be discouraged.

Whether the marijuana consumed by patients is of legal or illegal origin, for those who develop CUD, PCPs can implement SBIRT, a robust in-office program shown to reduce substance use harm. Psychotherapeutic and pharmacological options available for those patients who fail to respond to SBIRT are also summarized in this article.

Clinicians should teach their patients that cannabis is not a benign drug and it is not a safe plant to consume, especially for adolescents (Tables 10–14,17).[1,57,409,493,579] They should teach parents to protect children from accidental cannabis poisoning in homes where parents smoke pot.[580] They should emphasize to their adolescent and young adult patients to avoid driving or being in a car with a driver who is under the influence of cannabis smoking (Table 16).[581,582] Clinicians must understand that cannabis remains the never-ending, nefarious, nepenthe of the 21st century, which has great charm but major dangers for an uninformed global population.

Pied Piper: I attract attention
Chiefly with a secret charm…
Who doesn't know of the Pied Piper?
Alas, alas for Hamelin!....
They wrote the story on a column,

And on the great church-window painted
The same, to make the world acquainted
How their children were stolen away…"
The Pied Piper of Hamelin (Robert Browning: 1812–1889)

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On a bright morning they have fixed,
To seek the plain that southward lies.
Then from her task of twisting hemp,
See dancing through the mart she hies"
She King, Book of Ancient Poetry,
China, 2350 BC (1)

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