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Blurred Boundaries: The Therapeutics and Politics of Medical Marijuana

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Abstract

For 5 millennia, *Cannabis sativa* has been used throughout the world medically, recreationally, and spiritually. From the mid-19th century to the 1930s, American physicians prescribed it for a plethora of indications, until the federal government started imposing restrictions on its use, culminating in 1970 with the US Congress classifying it as a Schedule I substance, illegal, and without medical value. Simultaneous with this prohibition, marijuana became the United States' most widely used illicit recreational drug, a substance generally regarded as pleasurable and relaxing without the addictive dangers of opioids or stimulants. Meanwhile, cannabis never lost its cachet in alternative medicine circles, going mainstream in 1995 when California became the first of 16 states to date to legalize its medical use, despite the federal ban. Little about cannabis is straightforward. Its main active ingredient, δ-9-tetrahydrocannabinol, was not isolated until 1964, and not until the 1990s were the far-reaching modulatory activities of the endocannabinoid system in the human body appreciated. This system's elucidation raises the possibility of many promising pharmaceutical applications, even as draconian federal restrictions that hamstring research show no signs of softening. Recreational use continues unabated, despite growing evidence of marijuana's addictive potential, particularly in the young, and its propensity for inducing and exacerbating psychotic illness in the susceptible. Public approval drives medical marijuana legalization efforts without the scientific data normally required to justify a new medication's introduction. This article explores each of these controversies, with the intent of educating physicians to decide for themselves whether marijuana is panacea, scourge, or both. PubMed searches were conducted using the following keywords: *medical marijuana*, *medical cannabis*, *endocannabinoid system*, *CB1 receptors*, *CB2 receptors*, *THC*, *cannabidiol*, *nabilone*, *dronabinol*, *nabiximols*, *rimonabant*, *marijuana legislation*, *marijuana abuse*, *marijuana dependence*, and *marijuana and schizophrenia*. Bibliographies were hand searched for additional references relevant to clarifying the relationships between medical and recreational marijuana use and abuse.

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Very few drugs, if any, have such a tangled history as a medicine. In fact, prejudice, superstition, emotionalism, and even ideology have managed to lead cannabis to ups and downs concerning both its therapeutic properties and its toxicological and dependence-inducing effects.

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Marijuana is unique among illegal drugs in its political symbolism, its safety, and its wide use.

G. J. Annas[2]

Little about the therapeutics or politics of medical marijuana seems straightforward. Despite marijuana's current classification as a Schedule I agent under the federal Controlled Substances Act, a designation declaring it to have high abuse potential and "no currently accepted medical use,"[3] physicians and the general public alike are in broad agreement that *Cannabis sativa* shows promise in combating diverse medical ills. As with opium poppies before it, study of a drug-containing plant has resulted in the discovery of an endogenous control system at the center of neurobiological function whose manipulation has significant implications for the development of novel pharmacotherapies.[4]

As recreational use continues to be endemic in the United States and medical use of smoked cannabis burgeons, it becomes increasingly clear that the two are not discreet from each other, with implications medically for both seasoned and naive users. Even as proponents of legalization contend that smoked marijuana is a harmless natural substance that improves quality of life, a growing body of evidence links it in a small but significant number of users to addiction and the induction or aggravation of psychosis. As laboratory and clinical investigation exposes more of the workings of the recently discovered endocannabinoid system and potential pharmacologic applications show increasing promise, federal law puts a damper on almost any research. As an increasing number of states legalize marijuana's medical use, the federal government maintains its resolute stance that its use for any reason is criminal, a stance that renders prescribers simultaneously law-abiding healers and defiant scofflaws. In what has been called "medicine by popular vote,"[5] the states formulate medical marijuana statutes

based not on scientific evidence but on political ideology and gamesmanship.

In each of these respects—recreational vs medical use, benefit vs harm of use, laboratory research and pharmacologic application vs federal restrictions, and state vs federal law—boundaries blur. Contradictions and paradoxes emerge. This article explores each of these areas, with the intent of educating physicians so that they can decide for themselves whether marijuana is a panacea, a scourge, or both. PubMed searches were conducted using the following keywords: *medical marijuana*, *medical cannabis*, *endocannabinoid system*, *CB1 receptors*, *CB2 receptors*, *THC*, *cannabidiol*, *nabilone*, *dronabinol*, *nabiximols*, *rimonabant*, *marijuana legislation*, *marijuana abuse*, *marijuana dependence*, and *marijuana and schizophrenia*. Bibliographies were hand searched for additional references relevant to clarifying the relationships between medical and recreational marijuana use and abuse.

WHAT IS MEDICAL MARIJUANA?

For 5 millennia, *Cannabis sativa* has been used throughout the world medically, recreationally, and spiritually. As a folk medicine marijuana has been "used to treat an endless variety of human miseries," although typically under the aegis of strict cultural controls, according to DuPont.[7] The first medical use probably occurred in Central Asia and later spread to China and India. The Chinese emperor Shen-Nung is known to have prescribed it nearly 5 millennia ago. Between 2000 and 1400 BC, it traveled to India and from there to Egypt, Persia, and Syria. Greeks and Romans valued the plant for its ropelike qualities as hemp, although it also had medical applications. The medieval physician Avicenna included it in his formulary, and Europeans of the same epoch ate its nutritional seeds and made its fibers into paper, a practice that continued for centuries. Indeed, the American Declaration of Independence was purported to have been drafted on hemp-based paper.[8,9]

Traditional Eastern medicine met Western medicine when W. B. O'Shaughnessy, an Irish physician working in Calcutta in the 1830s, wrote a paper extolling "Indian hemp."[10] The list of indications for which he recommended cannabis—pain, vomiting, convulsions, and spasticity—strikingly resembles the conditions for which modern medical marijuana proponents extol its virtues. As of 1854, the medical use of cannabis received official legitimacy by its listing in the US Dispensatory.[11] The black leather bags of 19th-century US physicians commonly contained (among many other plant-based medicaments) cannabis tinctures and extracts for ailments ranging from insomnia and headaches to anorexia and sexual dysfunction in both sexes.[12] Cannabis-containing remedies were also used for pain, whooping cough, asthma, and insomnia and were compounded into extracts, tinctures, cigarettes, and plasters.[13,14] More recently, the Institute of Medicine issued a report based on a summary of the peer-reviewed literature addressing the efficacy of therapeutic marijuana use. The 1999 study found at least some benefit for smoked marijuana in stimulating appetite, particularly in AIDS-related wasting syndrome, and in combating chemotherapy-induced nausea and vomiting, severe pain, and some forms of spasticity.[15,16]

Contemporary Americans who eschew mainstream medical treatments while embracing herbal remedies perpetuate this 19th-century tradition of cannabis use. Even if cannabis use lacks the scientific legitimacy endowed by the randomized controlled trials that underpin modern evidence-based medicine, these individuals assert that the smoked herb is highly effective against "a vast array of diseases that are refractory to all other medications"[17] and requires no further study to prove its medical worth. Americans who shun prescription drugs but stock up on "natural" compounds in the vitamin section of their local grocery store are prime candidates for this long-established folk nostrum, an "organic" means of self-medication.

With gardening sections in bookstores displaying robust selections of manuals for cannabis cultivation, an uninformed shopper might conclude that growing marijuana is as legitimate in the United States as cultivating roses or zinnias. Anyone with a credit card has ready access to blueprints for marijuana propagation and culture. The concentration of δ-9-tetrahydrocannabinol (THC), the psychoactive ingredient in cannabis, ranges from less than 0.2% in fiber-type hemp (so-called ditch weed) to 30% in the flower buds of highly hybridized sinsemilla.[18] With the goal of achieving better, more intense highs, cannabis cultivators have crossed and recrossed diverse strains with the result that an average THC content of 2% in 1980 became 4.5% in 1997 and 8.55% by 2006.[19,20]

The term *medical marijuana* is ambiguous in that it can refer to 2 of the 3 forms in which cannabinoids occur.[18,21] These include (1) endocannabinoids, arachidonic acid derivatives such as anandamide produced in human tissue like any other endogenous neurotransmitters; (2) phytocannabinoids, the hundreds of compounds in the *C sativa* plant, including the 2 most medically relevant ones, THC and cannabidiol; and (3) synthetic cannabinoids, laboratory-produced congeners of THC and cannabidiol that form the foundation of the pharmaceutical industry in cannabinoid-related products.[21] For purposes of this review, *medical marijuana* will be synonymous with *botanical cannabis*, the second option,

as distinct from the third option, *pharmaceutical cannabinoids*, which are synthetic cannabinoid-based medications in use or under development.

Botanical cannabis attracts the notoriety and controversy. Given the far-flung influence of endocannabinoids throughout the body, it is not surprising that botanical cannabis has traditionally been used to combat so many ills. In modern times, it has become an option of last resort for those for whom available pharmaceuticals have proven ineffective, including individuals with intractable nausea and vomiting with cancer chemotherapy or anorexia in human immunodeficiency virus disease. This is the same substance, of course, that delights recreational users, blurring the boundary between health care and pleasure.

RECREATIONAL USE BLENDS INTO MEDICAL USE

For recreational users, access to marijuana has always been about getting intoxicated. In the 21st century, cannabis is the most widely used illicit drug in the world,[22] with the United Nations estimating that up to 190 million people consumed cannabis in 2007.[23-25] Alice B. Toklas's legendary brownies notwithstanding, smoke inhalation is the preferred method of ingestion.[20] Unlike eaten botanical cannabis, smoked botanical cannabis affords high bioavailability, rapid and predictable onset, and easy titration that allows the smoker to maximize desired psychotropic effects and minimize negative ones.[26,27] In what Russo calls an "entourage effect," other cannabinoid constituents of the smoke besides THC may enhance the high[28] or reduce the toxic effects of unopposed THC.[29] Under the influence of the inhaled drug, most users experience "mild euphoria, relaxation, and perceptual alterations, including time distortion and intensification of ordinary experiences such as eating, watching films, listening to music, and engaging in sex."[20] A few experience dysphoria, anxiety, even frank paranoia—symptoms that can also trouble medical users.[30] As cannabis strains are bred that amplify THC content and diminish counteracting cannabidiol, highs become more intense but so do degrees of anxiety that can rise to the level of panic and psychosis, particularly in naive users and unfamiliar stressful situations.[31-33]

Marijuana is touted as a kind of social lubricant, helping users relax and feel more expansive and less self-conscious. Effects that can limit use in a medical setting (short-term memory disruption, a sense of slowed time, increased body awareness, reduced ability to focus, incoordination, and sleepiness) are exactly the sensations recreational users prize.[21,34] Cohen[35] sums it up thus: "Can the recreational use of marijuana cause cognitive impairment? The most obvious answer is 'yes'—after all, this is the basic reason for its recreational use."

Whereas the psychoactive properties of cannabis were first recognized thousands of years ago, these mind-transcending qualities were valued primarily as religious adjuncts. In the West before the mid-20th century, recreational cannabis use was restricted to such fringe or marginalized groups as European intellectuals, rural Brazilian blacks and fishermen, and impoverished Mexicans for whom it was "the opium of the poor." Use became increasingly popular in African American and immigrant Hispanic neighborhoods before 1950. The "explosion of its consumption for hedonistic purposes" to the point that up to two-thirds of US young adults, transcending social class and race, had tried cannabis did not occur until the 1970s and 1980s.[12] This explosion happened not only among those getting high for fun but also in those seeking to treat protean medical conditions.

Medical and recreational users differ in how they use the drug. The amount used and goals of ingestion diverge.[36] The fundamental motivation (symptom relief) of the former does not match the goal (getting high) of the latter.[25] Nonetheless, several studies have demonstrated significant overlap between medical users and recreational users. In a Canadian study of 104 human immunodeficiency virus–positive adults, 43% reported botanical cannabis use in the previous year. Although two-thirds endorsed medical indications, ranging from appetite stimulation and sleep induction to antiemesis and anxiolysis, a full 80% of this group also used it recreationally.[37] Another team of Canadian investigators interviewed 50 self-identified medical cannabis users, finding that "typically medical cannabis use followed recreational use and the majority of those interviewed were long-term and sometimes heavy recreational users." Most medical users continued their recreational use.[38] One of the "protean" medical indications is even drug dependence itself. Although there is no research to support a substitution strategy, addicts attempting to reduce negative outcomes from alcohol, prescription drugs, or illicit drugs, such as opiates, may have switched to medical cannabis, regarded as a safer option than the substances on which they were formerly dependent.[39,40]

Blurring the boundary between medical and recreational use still further, interviews with more than 4100 Californians revealed that the medically ill prefer inhaling their medication. When taken in pill form, drug effects are harder to control and more likely to prove noxious or excessively prolonged.[26] Unlike smoked cannabis, swallowed cannabis undergoes first-pass hepatic metabolism, leading to variable and unpredictable amounts of active agent

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reaching target tissues. Absorption is more erratic and peak concentrations lower.[11] Smoked cannabis offers both rapid response and easy titration[35] based on the number of inhalations. In the manner of patient-controlled analgesia (the bedside narcotics pumps used in medical settings), smokers can dose themselves repeatedly throughout the day, inhaling enough THC to get analgesic benefit but not enough to sustain motor or psychoactive adverse effects that will dissipate rapidly, if they occur at all.[27,41] Medical users may actually consume less than recreational users, inhaling doses sufficient only to produce desired clinical effects for only as long as needed.[3] Vaporizers that heat cannabis enough to release cannabinoids but not the smoke and toxins generated with combustion have the potential to reduce respiratory symptoms and decrease negative effects on pulmonary function associated with burning the drug.[42,43]

Medical users have the added benefit of breathing in such other marijuana components as cannabidiol, purported to act synergistically with THC in both increasing benefits and reducing adverse effects.[44] THC-induced euphoria may also work synergistically with the drug's analgesic effects.[21] In contrast to the usual medical model, the patient rather than physician determines the correct dose. The physician's instructions to the patient may be as vague as telling him or her to smoke as much as needed.[45]

As with the Canadian studies, the California study found that medical use often "occurred within a context of chronic use." That is, those who favored smoked cannabis for medical purposes were kindly disposed toward the drug from previous recreational experience with it and were typically unperturbed by cognitive and euphoric adverse effects. Indeed, the combination of physical and emotional relief botanical cannabis provides may motivate the medically ill to continue using it.[26] Further confirming this relationship were the demographics that emerged from an English study of botanical cannabis use in individuals with chronic pain, multiple sclerosis, depression, arthritis, and neuropathy. Botanical cannabis users were significantly more likely to be young, male, and recreationally familiar with the drug ($P<.001$).[46] A recent California study of patrons of medical marijuana clinics found similar demographics: a sample that was three-fourths male, three-fifths white, and overwhelmingly familiar with cannabis from recreational use. Although men, whites, and African Americans were overrepresented, women, Latinos, and Asian Americans had disproportionately low representation.[47]

Botanical cannabis is clearly not for everyone. Multiple observers report that patients without recreational experience have difficulty tolerating its psychoactive adverse effects and ultimately refuse to continue using it.[28] Elikkottil et al[21] caution about drawing conclusions that botanical cannabis is only for "potheads," however, given that randomized controlled trials of botanical cannabis in inexperienced users have not been performed.

THE RELATIONSHIP BETWEEN PSYCHOSIS AND MARIJUANA

Marijuana continues to have the reputation among the general public as being benign, non–habit-forming, and incapable of inducing true addiction.[39,48] For most users this may be so. Experimentation with marijuana has become an adolescent rite of passage, with the prevalence of use peaking in the late teens and early 20s, then decreasing significantly as youths settle into the adult business of establishing careers and families. With a lifetime dependence risk of 9% in marijuana users vs 32% for nicotine, 23% for heroin, 17% for cocaine, and 15% for alcohol,[25] the addiction risk with marijuana is not as high as that for other drugs of abuse. Unlike cocaine dependence, which develops explosively after first use, marijuana dependence comes on insidiously.[49] Marijuana use typically starts at a younger age than cocaine use (18 vs 20 years of age). The risk for new-onset dependence is essentially zero after the age of 25 years, whereas cocaine dependence continues to accrue until the age of 45 years. Likewise, the average age at first alcohol use is the same as for marijuana, but alcohol users will keep on making the transition from social use to dependence for decades after first use.[49]

One in 11 users—1 in 6 for those starting in their early teens—is hardly an inconsequential percentage, however.[50] Like all addictive drugs, marijuana exerts its influence through the midbrain reward center, triggering dopamine release in the prefrontal cortex.[51] Although its existence was questioned until recently, a withdrawal syndrome is increasingly appreciated, characterized by irritability, anxiety, anorexia and weight loss, restlessness, disturbed sleep, and craving.[52]

DuPont[7] writes that "marijuana makes users stupid and lazy," citing an extreme amotivational syndrome characterized by listlessness and apathy in heavy smokers, not just when using the drug but all the time. The befuddled, endearingly dissolute stereotype, parodied in "stoner" movies like Cheech and Chong's *Up in Smoke*, is not what happens to most occasional users who experience only temporary mild perceptual changes accompanying a general sense of well-being and ease with the world. The disputed amotivational syndrome of heavy use resembles the negative symptom complex of schizophrenia.[53,54]

Using hospitalization as a proxy for serious psychiatric illness, Schubart et al[55] identified a dose-response relationship, with incidental users having 1.6 times the chance of hospitalization and heavy users 6.2 times the risk. "The association of cannabis use with psychiatric inpatient treatment is a clear indication of the association of cannabis use with mental illness," they wrote. More specifically and more ominously, those with a psychotic predisposition may respond to marijuana with more marked perceptual changes into which they have little insight, accompanied by elevations in hostility and paranoia.[56] Schizophrenia has been posited as a hypercannabinoid condition because schizophrenic patients have significantly elevated cerebrospinal fluid levels of anandamide, the most important endogenous cannabinoid.[57] Cannabis use has been implicated as a potential cause, aggravator, or masker of major psychiatric symptoms, including psychotic, depressive, and anxiety disorders, particularly in young people.[30,58,59] In underscoring the potential for psychosis, a longitudinal study of more than 50,000 Swedish conscripts has been influential. During a 27-year follow-up period, the more cannabis individuals had used in adolescence, the more likely they were to develop schizophrenia, with those who had used cannabis on more than 50 occasions nearly 7 times more likely to manifest the disease than those who had never used cannabis.[60]

This association between cannabis and psychosis notwithstanding, the question of whether cannabis causes psychosis remains unresolved, even as evidence mounts that its use worsens the course of psychotic illness. In an Australian cohort, Degenhardt et al[61] tested 4 hypotheses regarding the association between cannabis use and schizophrenia, including that cannabis use (1) may cause schizophrenia in some patients, (2) may precipitate psychosis in vulnerable individuals, (3) may exacerbate symptoms of schizophrenia, or (4) may be more likely in individuals with schizophrenia. They noted that during the last 3 decades of the 20th century, cannabis use had significantly increased in Australia without a corresponding increase in schizophrenia prevalence, an observation that gravitated against a simple cause-and-effect relationship between the two. However, they also found that cannabis use precipitated the onset of the disease in the vulnerable and exacerbated the course of the illness in those who already had it.

In a 2007 meta-analysis pooling 35 longitudinal, population-based studies, Moore et al[59] found an elevated odds ratio (OR) of 1.41 (95% confidence interval [CI], 1.20-1.65) for psychosis in individuals who had ever used cannabis. They also demonstrated a dose-response effect, with the OR increasing to 2.09 (95% CI, 1.54-2.84) for more frequent users, defined—depending on the study—as daily, weekly, or more than 50 times in their lives. A Dutch study[62] shows how this association plays out in actual numbers. For 3 years, van Os et al followed up 3964 psychosis-free individuals, 312 of whom used cannabis. During the observation period, 8 of the 312 (2.2%) developed psychotic symptoms, with 7 of the 8 (88%) having severe enough symptoms to justify receiving a full-fledged diagnosis. Of the 3652 nonusers, 30 (0.8%) developed symptoms, with only 3 of the 30 (10%) meeting criteria for a psychotic disorder. The risk was small in both groups but impressively elevated in users vs nonusers.

For individuals already diagnosed as having a schizophrenic spectrum disorder, ongoing cannabis use predicts a rockier course. Comparing 24 abusing and 69 nonabusing schizophrenic patients who were otherwise clinically indistinguishable, Linszen et al[63] found 42% of abusers vs only 17% of nonabusers experiencing psychotic relapse during the year-long study period ($P=.03$). Moreover, when they compared heavy users (>1 marijuana cigarette per day) with mild users (≤1 cigarette per day), they found an even more robust correlation, with 61% of the heavy users vs 18% of the mild users experiencing relapse ($P=.002$). The longer the period of cannabis use, the higher the risk of relapse. In a 10-year follow-up of 229 patients after first hospitalization for schizophrenia, Foti et al[64] demonstrated that the 10% to 18% who continued to use cannabis throughout the study period had a more severe course as measured by the intensity of positive psychotic symptoms. The association was bidirectional: cannabis smokers had worse psychosis, and the more intensely psychotic individuals were more likely to smoke cannabis.

van Os et al hypothesize that cannabis may exert its negative influence through causing dysregulation in the endogenous cannabinoid system that (among many other interactions) modulates dopamine and other neurotransmitter systems within the brain. They posit a "preexisting vulnerability to dysregulation" that accounts for why some individuals and not others respond to cannabis with psychosis.[62] Using contemporary epigenetic terminology, Henquet et al[65] attribute the greater psychosis risk in certain cannabis users to a synergy between gene (inborn susceptibility) and environment (exogenous trigger). Moreover, increasing evidence implicates a vulnerable developmental period—peripuberty—when cannabis use is more likely to cause trouble.

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DANGERS OF EARLY USE

Whereas adult users appear comparatively immune to cannabis-induced behavioral and brain morphologic changes, the same cannot be said of individuals initiating use during their early teens, when effects are both more severe and more long-lasting than in adults.[66] During puberty, a period characterized by significant cerebral reorganization, particularly of the frontal lobes implicated in behavior, the brain is especially vulnerable to adverse effects from exogenous cannabinoids.[58,67] How they interfere with this remodeling process during what Schneider[67] calls a "sensitive period" is unknown, although Bossong and Niesink[68] propose that exogenous cannabis use can induce schizophrenia during late brain maturation through physiologic disruption of the endogenous cannabinoid system that modulates glutamate and γ-aminobutyric acid release in prefrontal neurocircuitry, an iteration of the hypothesis of van Os et al. Furthermore, in keeping with the epigenetic hypothesis of Henquet et al, carriers of a specific polymorphism of the catechol oxidase methyltransferase gene (*COMT* valine 158 allele) are especially likely to develop psychotic symptoms or full-blown schizophrenia, an effect attenuated or eliminated if cannabis use is delayed until after brain maturity.[69]

Short of full-blown schizophrenia, many other persistent effects have been observed in heavy (defined as weekly or more often) pubertal users, including working memory deficits, reduced attention, reduced processing speed, anhedonia, abnormal social behavior, susceptibility to mood and anxiety disorders, and greater likelihood of dependence.[67,70] Kuepper et al[71] posit that ongoing cannabis use may increase psychotic disorder risk by making transient psychotic experiences in adolescent users persist to the point of becoming permanent.

A study from 6 European countries comparing the health and legal implications of cannabis initiation before the age of 16 years found it associated with higher levels of abuse not only of cannabis but also of other illicit drugs, higher rates of both physical injuries and psychosomatic symptoms, academic failure, and delinquency.[72] Poor academic achievement, deviant childhood and adolescent behavior, rebelliousness, and parental histories of substance abuse characterize those at highest risk of dependence.[20,73] Those who started using marijuana before the age of 12 years had nearly 5 times the hospitalization rate of those starting in their later teens. Moderate use after the age of 18 years was not associated with increased rates of mental illness, concluded Schubart et al.[55] Protective against dependence is adult age of initiation and low-to-moderate use, particularly when marijuana is ingested for therapeutic rather than recreational purposes.[66]

With regard to cannabis as a "gateway" drug, its regular or heavy use in adolescence is clearly associated with increased risk for both abuse and dependence on other illicit drugs.[44] Neither causality nor directionality has been proven, however. Cannabis use may simply be a marker for deviant behavior, with the tendency to advance to harder drugs the result of their simply being available.[39,44,74] In what has been called a "reverse gateway," cannabis use weekly or more often predisposes adolescent users to more than 8 times the risk of eventual tobacco use and progression to nicotine dependence.[75]

Schneider[66] reminds us that most adolescents who use cannabis do not experience harmful outcomes. Concerning psychosis specifically, Luzi et al[76] emphasize that only 3% of heavy users actually develop schizophrenia. Nonetheless, reducing or delaying cannabis use could postpone or even prevent 1 in 6 cases of new-onset psychosis.[60,77]

Adolescent cannabis use is also associated with depressive and anxiety disorders that emerge later in life.[44] In a cohort of Australian girls followed up for 7 years from the ages of 14 to 15 years, 60% had used cannabis by the end of the study and 7% were daily users. Although the presence of current depression and anxiety did not predict cannabis use, gravitating against a self-medication hypothesis, Patton et al[50] observed a dose-related risk of eventual depression and anxiety. Weekly use was associated with nearly double the risk (OR, 1.9; 95% CI, 1.1-3.3) of subjects later reporting anxiety or depression, and daily use corresponded with an OR of 5.6 (95% CI, 2.6-12). The authors were reluctant to attribute the increased risk to cannabis alone, observing that social consequences of frequent use, including educational failure, unemployment, and crime, could account—at least in part—for the psychopathology.

Even as Patton et al[50] did not find that depression or anxiety drove teens to smoke marijuana, some recreational users appear to use it in a manner suggestive of antidepressant or anxiolytic medications. Teens using cannabis to decrease anxiety frequently meet criteria for anxiety disorders before their cannabis dependence begins.[32] Bottorff et al[78] reported on 20 adolescents who used marijuana regularly, finding that these adolescents distinguished themselves from recreational users in that they smoked marijuana not primarily for enjoyment but rather for its capacity to relieve anxiety and lift mood, reduce stress, facilitate sleep, and lessen pain. They titrated their intake, often using several times a day and beginning and ending the day with smoking, and frequently using alone. "Unlike the spontaneity typically involved in recreational use," Bottorff et al write, "these youth were thoughtful and prescriptive with their marijuana use, carefully moni-

toring and titrating their use to optimize its therapeutic effect." "Unmet health needs" for them included access to legitimate treatment for depression, insomnia, and anxiety. The paradox of marijuana both inducing and relieving anxiety is reconciled by understanding that effects on anxiety levels are dose dependent.[32] Although deliberate self-medication bears little resemblance to getting high for the pleasure—and occasionally panic—of it, it brings its own dangers. Individuals with anxiety disorders who use marijuana, alcohol, or other drugs in this way are up to 5 times more likely to develop substance dependence than anxious individuals who do not self-medicate.[3]

In sum, marijuana offers the recreational substance abuse version of caveat emptor. Although cannabis is an enjoyable diversion for most, it is linked to self-medication, addiction, or mental illness in a few, particularly those who start young.[3]

DANGERS OF MEDICAL MARIJUANA

Those skeptical of botanical cannabis do not argue that it is necessarily bad. Rather they contend that the benefits of cannabis—particularly when smoked—remain scientifically unproven, not only on its own merits but also compared with other available treatments. They contend that the usual standards for evaluating pharmacotherapies have been largely side-stepped.[17] They want legitimate research. In a 2008 position paper, the American College of Physicians trod a middle ground between praising and demonizing botanical cannabis, stating it is "neither devoid of potentially harmful effects nor universally effective" and calling for "sound scientific study" and "dispassionate scientific analysis" to find the appropriate balance.[79]

Critics of botanical cannabis are less sanguine than the American College of Physicians. They assert that garden-grown cannabis is neither pure nor refined, standards Americans have come to expect in their medications. DuPont calls it "a crude drug, a complex chemical slush," composed of well more than 400 different chemicals from 18 different chemical families, with the smoke containing more than 2000 chemical compounds.[7] In the short term, cannabis can cause increased heart rate, vasodilation with decreased blood pressure (as outwardly manifested by bloodshot eyes), and dizziness.[4] Although the use of vaporizers can minimize toxic exposure,[42,43] cannabis smoke contains many of the same toxins found in tobacco smoke, a concern not for palliative use in the terminally ill but for long-term smokers who put themselves at risk for pharyngitis, rhinitis, asthma, bronchitis, emphysema, and lung cancer.[11,80,81] "The increasing cries for the release of smoked marijuana to treat a variety of medical problems [are] rich in anecdotal testimonies and lacking scientific validation," Schwartz and Voth[82] state, adding that "a wonder drug it isn't." Yet jurisdiction after jurisdiction has permitted the voters rather than researchers following standard US Food and Drug Administration (FDA) protocols to endorse its medical use. "Medicolegal and political issues tend to overshadow the science and the medicine of marijuana use."[83]

So what is already known about the therapeutic potential of cannabis and where might research go were there no proscriptions against studying the plant?

THE ENDOCANNABINOID SYSTEM

Although cannabis has been part of the world's herbal pharmacopoeia for millennia, next to nothing about its mechanisms of action was known until the last half century. As with all folk medicines, practitioners established the therapeutic benefits and risks of their plant-derived remedies through careful observation. In this respect, the cannabis story mirrors that of the Oriental poppy, *Papaver somniferum*, the source of opium, which was appreciated both as a renowned painkiller and a tantalizing drug of abuse for thousands of years before its active agent, morphine, was identified in modern times along with opioid receptors, endogenous opioids, and an internal opioid system. "In both instances," write Baker et al,[4] "studies into drug-producing plants led to the discovery of an endogenous control system with a central role in neurobiology."

Modern scientific study of cannabis commenced with the isolation and structural elucidation of THC in 1964.[51] Not until 1990 was the cannabinoid receptor with which THC interacts, CB1, cloned,[84] and it was 1992 before anandamide, the endogenous ligand corresponding to THC and binding to CB1 receptors, was discovered.[85] Since then, an additional cannabinoid receptor, CB2, has been identified, and the 2 receptors have been found to have disparate distributions and functions in an endocannabinoid system that extends far and wide within the body as a physiologic modulator not only of the central nervous system but also of the autonomic nervous system, immune system, gastrointestinal tract, reproductive system, cardiovascular system, and endocrine network.[30,86]

Described as a "ubiquitous network in the nervous system"[87] that regulates synaptic neurotransmission in both excitatory and inhibitory circuits,[4] the endocannabinoid system is a finely tuned physiologic modulator, an "integral part of the [body's] central homeostatic modulatory system"[10] acting to regulate neurotransmitter release at the level of the synapse.[88] It functions in parallel and in conjunction with adrenergic, cholinergic, and dopaminergic systems in both the central and autonomic nervous

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systems, with influence on functions as disparate as blood pressure and bone growth.[30,51,84,88] In a specific organ system such as the gut, in which the endocannabinoid system is increasingly understood to have a complex and ubiquitous presence, regional variation in receptor distribution and organ-specific actions can influence functions as diverse as regulation of food intake, visceral sensation, gastrointestinal motility, gastric secretion, intestinal inflammation, and cell proliferation, to list only some.[89] CB1 receptors with their psychoactive potential are found in the central nervous system and widely distributed throughout the gut.[89] CB2 receptors essentially reside only in the periphery, where their activity is intrinsic to cellular and humoral responses related to neuroinflammation and pain,[86] as well as the critical gastrointestinal functions of digestion and host defense.[89]

The most common G protein–coupled receptors in the central nervous system (CB1 receptors) concentrate in specific brain areas that govern pleasure, movement, learning and memory, and pain, including the frontal cortex, basal ganglia, hippocampus, and cerebellum.[76] In the mesolimbic reward center, they reinforce pleasurable activities via anandamide, the endogenous cannabinoid that subtly regulates dopamine release. Exogenous plant-derived THC is a sledgehammer compared with anandamide's delicate chisel, the former causing marked disruption of neuronal signaling and circuit dynamics in the finely tuned endogenous system[36,88] and inducing addiction in the susceptible.[51] The presence of CB1 receptors in the cerebellum and basal ganglia explains both positive and negative influences of cannabinoids on motor tone and coordinated movement, including THC-induced discoordination or clumsiness in recreational users on the one hand and amelioration of spasticity in upper motor neuron diseases such as multiple sclerosis on the other.[87,88] Through their actions in the hippocampus, CB1 receptors modulate mood, and through activity in both the hippocampus and prefrontal cortex, they influence many elements of cognition, including concentration, short-term memory processing, attention, and tracking behavior.[20,73,87] They influence vegetative functions at the hypothalamic level; "the munchies," to which recreational marijuana smokers are prone and for which medical marijuana is prescribed, result from THC stimulation of CB1 receptors that govern food intake.[89] Nociception is modulated via spinal cord dorsal primary afferent tracts, central components of pain pathways whose manipulation by THC gives rise to its vaunted analgesic capacities. CB1 receptors modulate the activity of dopaminergic neurons that project to the prefrontal cortex from the brainstem reward center, thereby factoring in susceptible individuals into cannabis abuse and dependence.[90] Of note, due to the near absence of brainstem CB1 receptors, the drug spares the autonomic nervous system, no matter how much is ingested, with the result that a lethal overdose in humans has never been reported.[4,87] They are distributed so widely, however, that activating for one purpose can cause indiscriminate activation and a host of unwanted adverse effects throughout the body, a major challenge for pharmaceutical development.[84]

PROMISING PHARMACEUTICAL APPLICATIONS

In the rapidly growing field of endocannabinoid pharmacology, the potential for designing pharmacologic interventions is as broad as the endocannabinoid system's bodily distribution.[91] "Perhaps no other signaling system discovered during the past 15 years is raising as many expectations for the development of new therapeutic drugs, encompassing such a wide range of potential strategies for treatments," Di Marzo[92] writes. Describing the endocannabinoid system as "having pleiotropic homeostatic function," he asserts that salutary effects will come from many strategies, including drugs engineered to act as agonists or antagonists through both direct and indirect means, as well as agents to increase synthesis, reduce reuptake, or decrease degradation of endocannabinoids in neuronal synapses.[30] Medications active as analgesics, muscle relaxants, immunosuppressants, anti-inflammatories, appetite modulators, antidepressants, antiemetics, bronchodilators, neuroleptics, antineoplastics, and antiallergens are all possible as a consequence of this "pleiotropic" endocannabinoid system lending itself to manipulation through so many pathways.[92] Di Marzo conceptualizes the overarching pharmaceutical goal as "increasing or decreasing the tone of the endocannabinoid system while keeping side effects at bay."

More recently, researchers have stated that the power of new pharmacologic products will obviate the need for botanical cannabis. Izzo and Camilleri[93] envision "selective modulation of the endocannabinoid system in humans using modern pharmacological principles." Whereas botanical cannabis may be justifiable for experienced users with terminal illness and a tolerance for its psychoactive effects, particularly while awaiting these new drugs, Kalant[28] argues that future advances will result from developing highly selective, pure pharmaceuticals taken orally to bypass the health consequences of smoke exposure.[17,28]

Examples of specific strategies include using cannabinoid receptor agonists to increase gut motility in conditions such as ileus and using antagonists to decrease motility in inflammatory bowel dis-

ease.[93,94] Cannabinoid receptor agonists could also reduce inflammation peripherally through CB2 agonist activity.[95] Although mechanisms are poorly understood, cannabinoid agonists have shown promise in the laboratory as antineoplastic agents, with demonstrated antitumor effects including decreased angiogenesis, decreased metastasis through interference with cell migration, inhibited carcinogenesis, and attenuated inflammation.[94] Cannabinoid receptor antagonists could reverse the low blood pressure found in hemorrhagic shock, septic shock, and cirrhotic liver failure.[84]

The relationship between cannabis use and psychotic illness remains unsettled, even as hypothesized dysregulation of the endocannabinoid system in a number of psychiatric disorders has implications for developing treatments capable of manipulating relevant brain regions.[61,90,96] Given the increased density of CB1 receptors in the prefrontal cortex of schizophrenic patients[90] and the potential role of central CB1 receptor agonists such as THC in the production of schizophreniform illnesses,[30] the experimental CB1 receptor antagonist SR141716 has shown potent antipsychotic activity acting like an atypical antipsychotic.[54] Cannabidiol has also demonstrated antipsychotic properties without extrapyramidal adverse effects through poorly understood actions on both cannabinoid and noncannabinoid receptors.[30,91] In the cases of both SR141716 and cannabidiol, it is unclear whether they exert their influence directly via the CB1 receptor or indirectly through CB1 modulation of the dopaminergic and glutaminergic systems believed to be involved in the cognitive and behavioral impairments of schizophrenia. Regardless, each shows promise as a novel agent for treating psychotic disorders.[54]

Speaking to the broad promise of cannabinoid-based pharmaceuticals, Ben Amar[11] writes that "for each pathology it remains to be determined what type of cannabinoid and what route of administration are most suitable to maximize the beneficial effect of each preparation and minimize the incidence of undesirable reactions." Further understanding of the workings of the endocannabinoid system will continue to shed new light on disease processes.[21] The goals of research should be to identify the best strategies for exploiting the endocannabinoid system's physiologic and pathophysiologic effects and fashion pharmaceuticals accordingly.[5]

CURRENTLY AVAILABLE PHARMACEUTICALS

To date, only 4 pharmaceutical cannabinoids have been marketed. The first and second (dronabinol and nabilone) have been available in the United States since 1985 and a third one (nabiximols) in Canada since 2005.[36] A fourth (rimonabant) has shown promise treating nicotine dependence and reducing appetite in obese individuals. Available in Europe since 2006, the FDA failed to approve its release in the United States over concerns it can induce depression and suicidal behavior.[36,84,90]

The 2 US agents are CB1 receptor agonists, based on cannabis' primary psychoactive component, THC. FDA approved since 1985,[97] dronabinol (Marinol), a Schedule III controlled substance, is synthetic THC indicated for treating chemotherapy-induced nausea and vomiting and AIDS-related anorexia and wasting. With similar indications, nabilone (Cesamet) is a synthetic analog of THC. Dronabinol's therapeutic effect unfolds gradually for 30 to 60 minutes and lasts up to 6 hours. At 60 to 90 minutes, nabilone takes longer to act but persists as long as 12 hours.[14]

Even though the antiemetic efficacy of both dronabinol and nabilone equals or exceeds that of phenothiazines, their use is limited by the narrow gap between effective therapeutic doses and doses that cause such adverse effects as euphoria, dysphoria, cognitive clouding, drowsiness, and dizziness that are particularly problematic in naive users, whether smoking marijuana or taking oral pharmaceuticals.[11,44,88,98] The irony, of course, is that the "high" for one class of users is the "acute toxic effect" for another.[30] Moreover, because of variable absorption and first-pass kinetics, pharmaceutical cannabinoids achieve unpredictable blood levels, delaying both onset and cessation of therapeutic action while making the elusive therapeutic but nontoxic blood level that much harder to achieve. Interest in these agents has waned for arresting nausea and emesis with the advent of 5-HT_3 receptor antagonists like ondansetron that have greater potency, minimal psychotropic effects, and intravenous capabilities.[11]

Playing the devil's advocate, Ware and St Arnaud-Trempe[99] question why dronabinol or nabilone would ever be preferable to inhaled THC, given their adverse effects and delayed onset of action and botanical cannabis' lower cost and readier availability. Although the delayed onset is problematic when treating acute nausea, these pharmaceutical cannabinoids may have a therapeutic edge over other oral agents in managing delayed nausea and vomiting or preventing it altogether.[17,21,29,100] Wilkins[27] and Turcotte et al[14] emphasize that pharmaceutical cannabinoids should not be first-line therapies when better tolerated and more effective agents exist. For an indication such as emesis, dronabinol or nabilone is best reserved for cases resistant to standard therapies.[14]

Cannabidiol, the other important component found in botanical cannabis, is distinguished by its multiple peripheral mechanisms, including interaction with vanilloid receptors, modulation of adenosine signaling, interference with proinflammatory

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cytokines, and both immunosuppressant and antioxidant activity.[33] Cannabidiol lacks psychoactivity and may mitigate the anxiety and paranoia THC can induce, particularly in naive users. Mounting evidence suggests that the 2 cannabinoids work synergistically through an "entourage effect," with their interaction reducing the noxious effects of unopposed THC.[29,90] Moreover, through nonreceptor actions, cannabidiol has shown promise in its own right in the central nervous system as a possible anxiolytic and antipsychotic agent, as well as an anticonvulsant and neuroprotective agent.[56,76,91]

In Canada, an additional agent not yet available in the United States (but currently in phase 3 trials) more closely approximates the beneficial delivery method of smoked cannabis absent some of the risks, including tolerance, withdrawal, and high abuse potential.[21,25] With indications for cancer pain and neuropathic pain in multiple sclerosis, nabiximols (Sativex) is a mouth spray that contains both THC and cannabidiol in liquid form to take advantage of the modulatory interaction between the two.[10,39] Administered as an oromucosal spray, nabiximols uses a novel delivery method, absorption through the buccal mucosa, with the rapid-onset advantage of inhaled cannabis and the obvious benefit of controlled and regulated delivery but without such deleterious effects of smoking as sedation and memory impairment.[101]

Rapid uptake notwithstanding, a clinically significant difference between botanical cannabis and nabiximols is the latter's reduced bioavailability. With peak plasma THC concentrations nearly 20 times lower than with smoked cannabis, nabiximols flattens the steep-slope pharmacokinetic profile found in botanical cannabis, with corresponding reductions in adverse psychotropic effects.[25,29] It is this pharmacokinetic divergence from botanical cannabis that reduces the likelihood of nabiximols inducing dependence.[14,25] The nabiximols story underscores how a pharmaceutical that contains the same active ingredient as smoked cannabis can have disparate therapeutic effects stemming from divergent modes of administration and dissimilar amounts of absorbed THC and cannabidiol.[14,36]

FEDERAL BARRIERS TO CANNABIS RESEARCH

For nearly a century, cannabis was a part of the American pharmacopeia,[83] but by the 1930s, its days as a legitimate treatment were numbered. The flames of popular fear had been fanned for decades by the popular press[102] and by the likes of such high-camp films as the 1936 *Reefer Madness*, which hysterically portrayed "marihuana" as a threat to Western civilization through its purported capacity to induce user insanity and incite societal mayhem. In a standoff foreshadowing the current medical-political gridlock, the Federal Bureau of Narcotics over the objection of the American Medical Association pushed for the congressional passage of the 1937 Marihuana [sic] Tax Act that taxed cannabis at $1 an ounce when taken medicinally, $100 an ounce when used for unapproved purposes.[11] Musto[102] contends that the law was actually meant to placate xenophobic law enforcement officials and legislators from southwestern and western states who associated marijuana's use with "degenerate Mexicans and migrant workers", feared as a locus of crime and "deviant behavior." Pharmaceutical companies opposed any regulation.[102] In 1942, its removal from the US Dispensatory after nearly a century stripped it of any remaining therapeutic legitimacy.[47]

Not until 1970, however, citing marijuana's potential for abuse and addiction, did the US Congress finally declare it to have no medical value, rendering illegal a plant that had been used medicinally throughout the world for thousands of years.[51,83] Ironically, given the recent hue and cry over medical marijuana having been legalized without scientific input, the US Congress had failed to follow its usual review process dictated by the Controlled Substances Act that requires scientific evaluation and testimony before legislative action. It declared cannabis illegal in the absence of such evidence.[13]

With cannabis declared to have "no currently accepted medical use," the FDA designated it a Schedule I drug, a categorization reserved for street drugs with high abuse potential, such as heroin, quaaludes, lysergic acid diethylamide, and 3,4-methylenedioxymethamphetamine.[3] This designation has resulted in a near-cessation of scientific research on cannabis in the United States, particularly because the only federally authorized source of cannabis is a strain grown at the University of Mississippi and accessible to researchers only by applying to the National Institute on Drug Abuse,[103] which is reluctant to support medical research and has historically focused its efforts (almost) exclusively on demonstrating the drug's harmful effects.[14] According to Ware et al,[46,81,99] most cannabis research in the United States occurs "under a paradigm of prohibition and the study of risk is not yet balanced by much-needed research on benefits."

In challenging the one-sided devaluation of cannabis as a dangerous substance, Cohen[35] emphasizes that medical decision making is not based on risk alone. "The linchpin for medical decision-making is not *risk*—for no treatment is without risk—but the *balancing of risks and benefits*." Any rational consideration of legalizing medical marijuana should thus include both sides of the equation. Martin[17] writes that the "basic principles of medicine should take precedence over political expediency in

the development of a rational strategy for any therapeutic agent, even one as controversial as marijuana." Marijuana being relegated to Schedule I status appears especially irrational when precedence exists for assigning potential drugs of abuse Schedule II status when they also possess manifest medical benefits. Opioids, including morphine, are derived from the sap of *P somniferum,* the opium poppy. Widely abused in forms ranging from intravenous heroin to oral oxycodone, opioids nonetheless remain in other forms the most potent painkillers in the legitimate pharmacologic armamentarium. Cocaine, a product of the leaves of the *Erythroxylum coca* plant, likewise has ongoing utility as a topical anesthetic and vasoconstrictor. Closely related structurally to methamphetamine, a scourge among drug abusers in broad swaths of rural America,[104] psychostimulants such as methylphenidate and dextroamphetamine are treatment mainstays for attention-deficit/hyperactivity disorder. All these drug classes, plus barbiturates and sedative-hypnotics such as benzodiazepines, have high abuse potential but also important legitimate medical roles. "Their addicting liability alone has not automatically been allowed to contraindicate their use," states Cohen.[35] Readily available for laboratory scrutiny, the medically active ingredients have been isolated and purified so that physicians can prescribe them "free of a hodgepodge of inactive and potentially harmful substances."[7]

The involvement of an alphabet soup of federal agencies with divergent missions creates a series of potential barriers because several have the power to veto proposed initiatives.[105] The FDA, for example, authorizes research to proceed on safety and efficacy, the National Institute on Drug Abuse provides the research material, and the Drug Enforcement Agency grants the investigator the actual license to perform the research. Any one of these agencies has the power to halt an initiative in its tracks.[15] As described earlier in this article, the political climate at the federal level has essentially quashed the type of research that is routine before commercial introduction of new drugs. Ironically what Cohen[15] calls "federal intransigence" toward cannabis continues, even as knowledge about the substance—most generated in research laboratories outside the United States in countries, such as Canada, that legalized medical botanical cannabis in 2006—has advanced to the point that the drug and its interactions with the endocannabinoid system can actually be studied biochemically.[11,77] Moreover, the intransigence perpetuates what Aggarwal et al[10] label a "translational gap" between "patient-centered medicine" as manifested in the public's wide support and use of botanical cannabis and the research-driven scientific knowledge that cannot accrue until federal prohibitions on research are lifted. Ill-informed practitioners are thus left to make do with anecdotal testimony and case reports—the least rigorous form of evidence—to guide their prescribing.[10] The current catch-22 is that the cannabis that should be studied—diverse strains hybridized by entrepreneurial drug dealers—is illegal and the cannabis that can be legally studied—the decades-old Mississippi strain—is essentially kept off-limits.

It is a judicial fluke that the National Institute on Drug Abuse has provided medical marijuana to a handful of patients (never more than 32, currently 4 surviving) as the outcome of the settlement in a lawsuit pressed in 1976 by a man with cannabis-responsive glaucoma. That settlement became the basis for the FDA's Compassionate Investigational New Drug Study program for patients with marijuana-responsive conditions. No patient has been enrolled since 1992, when the George H. W. Bush administration suspended new registration in reaction to a large influx of applications from AIDS patients.[106,107]

STATES' DEFIANCE OF FEDERAL LAW

Meanwhile, in the legal arena, the federal government pits itself against increasing numbers of states—16 plus the District of Columbia—with regulations permitting botanical cannabis use for certain chronically or critically ill patients that contradict federal law.[10] A consequence of the discrepancies between federal and state statutes is that users and purveyors of botanical cannabis for any purpose can be arrested and charged with federal crimes, even in states where possessing small quantities or growing one's own stash for medical use is legal. In the absence of an overarching federal approach, these states lack consensus on what constitutes physician authorization, which patients qualify for treatment, and how they can acquire their botanical cannabis, creating what is essentially a "regulatory vacuum."[3,15] Possession limits, for example, range from 1 oz and 6 plants in Alaska and Montana to 24 oz and 24 plants in Oregon.[108] Some state laws are remarkably lax. For example, when California became the first American state to legalize botanical cannabis in 1996, it allowed wide latitude for its use, permitting physicians to prescribe it not only for serious medical illnesses but also "for any other illness for which marijuana provides relief," including such emotional conditions as depression and anxiety, a state of affairs that has "maximally broaden(ed) the range of allowable indications."[26] Moreover, no provision of the law defines what constitutes a bona fide patient-physician relationship.[15] An estimated 250,000 to 300,000 Californians have garnered physician approval, a number that belies botanical cannabis being provided only to the seri-

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ously ill and dying. A new industry has arisen around cultivating and dispensing medical marijuana to the hundreds of thousands of individuals authorized to use it.

Organized medicine continuing to condemn the federal government for its stance toward medical marijuana drives the ongoing legislative and scientific chaos. The American Medical Association, the Institute of Medicine, and the American College of Physicians contend that the "patchwork of state laws" do little to "establish clinical standards for marijuana use"[3] and have called for reclassification of cannabis as a Schedule II controlled substance so researchers can follow "the principles that are used to evaluate all other pharmacotherapies [that] have largely been ignored for medical marijuana." These principles include pharmaceutical companies petitioning the FDA for the right to put new compounds through a battery of tests in animals and humans that ensure that the drug's benefits outweigh its risks,[79] determining precise dosing regimens, seeking FDA approval for the proposed new drug, and manufacturing unadulterated active drug to high standards. Until this change occurs, a redesignation that would acknowledge not only its abuse risks but also its therapeutic benefits, the "rigorous scientific evaluation" that underpins pharmaceutical regulation in the United States cannot proceed.[3]

CONCLUSIONS

Given cannabis' worldwide use for thousands of years for medical and spiritual purposes, the contemporary American tumult over medical marijuana seems peculiar and misguided. Despite cannabis being part of the US pharmacopeia through much of the 19th and early 20th centuries, a federal government deeply suspicious of mind-altering substances began imposing restrictions on its prescription in the late 1930s, culminating in 1970 when the US Congress classified it as a Schedule I substance, illegal, without redeeming qualities.

Despite its illegality, cannabis has in the latter half of the 20th century become the most abused illicit substance in the United States. For most individuals, recreational cannabis use is essentially harmless, a rite of passage ending as young people settle into careers and adult intimate relationships.[20,109,110] For 10%, however, the drug becomes addictive, its relaxing properties transforming into a constant need that interferes with interpersonal and occupational advancement. For an even smaller proportion—those with a predisposition toward psychotic illness—it may abet the earlier emergence of psychosis and a rockier illness course if use persists.

Prohibition notwithstanding, cannabis' recognized medical uses never went out of favor in alternative medicine circles. Its therapeutic properties have been particularly favored by former recreational users familiar with its psychoactive effects, some of whom blur boundaries by continuing to use it recreationally. In the 1980s, it was found effective for treating severe nausea induced by cancer chemotherapy and cachexia in AIDS patients. The first cannabinoid-based pharmaceuticals—dronabinol and nabilone—came into medical use in 1985. Without an understanding of how these medications worked, they were prescribed empirically. As the mysteries of the endocannabinoid system were unraveled during ensuing decades, however, a rationale for both its recreational and sweeping medical effects has emerged.

The natural next step—pharmaceutical development—has been thwarted by the federal government's seeming unwillingness to have new scientific discovery supplant long-standing ideology. Bureaucratic hurdles not erected for other potential pharmaceuticals continue to interfere with legitimate cannabis research. The federal government instituted its 1970 ban in the absence of scientific evidence supporting its position. It maintains the ban, despite scientific evidence suggesting that cannabis could have positive effects on the many organ systems endocannabinoid activity modulates.

Although remaining at risk of arrest on federal charges, medical users have increasing latitude as more and more states endorse botanical cannabis. In defiance of a federal ban that appears increasingly irrational, 16 states and the District of Columbia have legalized botanical cannabis' medical use. Without a federal umbrella, regulations lack any state-to-state uniformity about what constitutes acceptable indications, appropriate prescriber-patient relationships, or legitimate means of acquiring botanical cannabis. In such states, physicians who prescribe medical marijuana are susceptible to prosecution under the same statutes as drug dealers.[111] Public approval and political expediency rather than scientific data drive the continued implementation of these state laws.

Like alcohol imbibers during the prohibition era in the United States, recreational users continue to smoke cannabis illicitly, as they have always done. Because of this modern-day prohibition, opportunities to further study marijuana's risks and benefits and develop new pharmacotherapies are squandered. In passing their own regulations endorsing medical marijuana use, states defy the federal government. In each of these instances, boundaries among the legal, social, and medical realms blur. Depending on context, marijuana can thus be panacea, scourge, or both.

It is high time for the federal government to acknowledge and accept this "both-ness" by reclas-

sifying marijuana so that it has the same status as certain opiates and stimulants. The Schedule II classification of these pharmaceuticals countenances not only a healthy respect for their addictive potential but also a robust appreciation for their medicinal value.[112] By forcing marijuana to languish as a Schedule I drug with a "high potential for abuse, no accepted medical use, and no accepted safety for use in medically supervised treatment,"[104] the federal government thumbs an illogical nose at contemporary public sentiment, recent scientific discoveries, and potentially head-to-toe therapeutic breakthroughs. This reclassification would be a first step toward reconciling federal and state law and permitting long-stifled research into a potential trove of therapeutic applications to commence.

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