What Should We Tell Our Patients About Marijuana (*Cannabis indica* and *Cannabis sativa*)?

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Abstract

With several states allowing medicinal use of marijuana and a growing number decriminalizing recreational use, many of our patients are using this herbal drug. Approximately 43% of US adults have tried marijuana, with 13% using it regularly. These users are seeking help from integrative medicine practitioners regarding safety. They are looking for advice based on research and clinical experience, not politics or philosophical bias. The major health problems caused by marijuana appear to be bronchial irritation, decreased motivation, learning difficulties, and injuries. However, less well appreciated are the toxicity problems caused by contamination with pesticides and solvent residues. We have important guidance to help prevent unnecessary toxicity in our patients who choose to use marijuana. This editorial reviews toxicity and safety. Medicinal use will be addressed in the future.

Long-time readers of *IMCJ* are well aware of the many editorials I have written on how a growing body of research is showing that toxins have become a major cause of chronic disease. As I study toxicity, my understanding has broadened to include not only environmental metals and chemicals but also endogenously produced toxins such as those from homocysteine, gut bacteria and nonoptimally detoxified hormones. To this list I now add what I call "toxins of choice." Few of our patients are intentionally exposing themselves to neurotoxic organophosphate pesticides, endocrine disrupting polychlorinated biphenyls (PCBs), insulin receptor site-blocking phthalates, or lung-damaging mold from damp buildings. However, many of our patients are intentionally consuming known toxins such as alcohol and marijuana and are unlikely to realize that at modest dosages, salt, high-fructose corn syrup, phosphates, and nonsteroidal anti-inflammatory drugs (NSAIDs) are toxic as well. Added to this that by also considering genetic susceptibility, even sources of gluten, can be toxic. The huge load of environmental, endogenous, and choice toxins add up to deplete stores of protective glutathione and cause physiological and structural damage in many ways.

Table 1 shows my current list of the many toxins that stress physiology and cause disease in our patients. Where I have written an editorial on the topic, the issue is included in parentheses.

Cannabis (Marijuana)

Although the federal government has classified *Cannabis* as a controlled substance illegal for use, many states have now decriminalized its use. Twenty-four states and the District of Columbia have passed laws allowing medicinal use of marijuana and 14 states have decriminalized its use. The percentage of Americans who say they have tried marijuana has steadily increased from 4% in 1969 to 43% in 2016.[1]

Cannabis production has become a multibillion dollar industry in the United States, and legal markets for cannabis are projected to reach $11 billion by 2019.[2] The federal illegality of *Cannabis* has resulted in not only limited clinical research but also a production environment with few standards and very little regulation. As most is currently grown indoors, heavy use of agricultural chemicals is common. Toxicity may be due to not only constituents of marijuana itself, but also contaminants such as solvents, pesticides, and heavy metals with most extracts adding solvent residues. This likely helps explain some of the discrepancies in the research.

Toxicity

Unadulterated Cannabis

Almost 500 compounds have been extracted from *Cannabis*, of which 65 are classified as cannabinoids. The most abundant cannabinoids include delta-9-tetrahydrocannabinoic acid (THCA), cannabidiolic acid (CBDA), cannabigerolic

Table 1. The Many Sources of Toxins

Exogenous Toxins	**Endogenous**	**Toxins of Choice**
OTC and prescription drugs (see editorial in *IMCJ* 7(3))	Catecholamines, if COMT SNP	Alcohol (see editorial in *IMCJ* 11.(6))
Chemicals	Gut-derived toxins	Marijuana (see editorial in *IMCJ* 15(6))
Inorganic	Homocysteine (see editorial in *IMCJ* 6(4))	Food constituents
Organic	Non-end product metabolites	High-fructose corn syrup
Fluoride	Poorly detoxified hormones	Phosphates
Persistent organic pollutants (see editorial in *IMCJ* 12(2))		Salt (see editorial in *IMCJ* 14(1))
Solvents		Smoking
Metals		Wheat, if zonulin producer (see editorial in *IMCJ* 12(6))
Arsenic		
Cadmium		
Lead		
Mercury (see editorial in *IMCJ* 8(1), 8(2), 9(4))		
Microbial		
Mold (damp building, 15.2, 15.3)		
Particulate matter		
Radiation		
Light at night		
Medical		
Cell phone		

acid (CBGA), and their decarboxylated derivatives delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabigerol (CBG).[3] These compounds are converted into their more active decarboxylated counterparts by heat (smoking, evaporation, baking), light, or natural degradation. THC is the most psychoactive component of cannabis and alters cognition primarily through the activation of CB_1 receptors on presynaptic axons, though several other mechanisms have been identified.[4,5] The content of THC in marijuana has increased from 3.1% in 1992 to 5.1% in 2002.[6,7]

THC itself has low toxicity and modest use has shown minimal long-term physical or psychological effects—when not used to excess.[8,9] Acute high dose intoxication occurs quickly but is short term. Typical symptoms include nausea, anxiety, paranoia, short-term memory loss, confusion, and disorientation.[10] THC impairs gonadal function by blocking gonadotropin-releasing hormone (GnRH) release. This results in lower levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which causes reduced testosterone production by the testicular Leydig cells.[11]

The research on the toxicity of whole plant marijuana is inconsistent—probably due to lack of control for contaminants, poor assessment of dosage, small sample sizes, limited number of heavy users, mode of use, and not adjusting for other factors such as alcohol, tobacco, and other recreational drugs.[12]

The method of use significantly affects the toxicity of marijuana. The most common use is inhalation of the smoke of the dried plant. This results in higher risk for adverse effects.[13] The whole-plant smoke contains many hazardous compounds such as ammonia, cyanide, heavy metals, carbon monoxide, mutagens, carcinogens, and polycyclic aromatic hydrocarbons.[14] Surprisingly, the tar from a *Cannabis* cigarette contains higher concentrations of carcinogens such as benzanthracenes and benzopyrenes than does tobacco smoke.[15]

Contaminants

Pesticides. For most of the 20th century, the majority of marijuana produced in the United Sates was grown outdoors. With more aggressive law enforcement, marijuana agriculture moved indoors. Although this provided the benefit of year-round cultivation, it also required the use of agricultural chemicals, typically synthetic fertilizers and pesticides.

Because *Cannabis* cultivation is illegal, there are no pesticides registered for use on *Cannabis* in the United States, meaning there is little research on their use for this purpose.[16] The limited research suggests that this results in higher chemical residue levels.[17] There are apparently no direct studies on how pesticides in *Cannabis* affects consumers of the product. Table 2 shows a list of the toxic contaminants that have been found in in both medical and

Table 2. Toxic Agricultural Chemicals Found in Cultivated Marijuana[19,20,21,22]

Pesticides	Bifenthrin, chlorpyrifos, diazinon, methamidophos, teflubenzuron
Fungicides	Tebuconazole
Growth regulator	Ethephon
Mosquito repellant	DEET, Malathion

Abbreviation: DEET, *N,N*-diethyl-meta-toluamide.

recreational marijuana. Research has shown that *Cannabis* extracts (see Solvents section below) contain considerable amounts of pesticides.[18]

Solvents. Many methods are used to concentrate the active constituents in *Cannabis*. The organic solvents benzene, hexane, naphtha, petroleum ether, and butane pose a significant risk of toxic chemical concentration.[23] Hexane and benzene are neurotoxic, and naptha and petroleum ether are potential carcinogens. Research has shown significant residues in these products.[24] A process called *dabbing* uses butane to produce higher THC content.[25]

Safer alternative methods of concentration use ethanol and olive oil. Perhaps best is the use of supercritical CO_2 to extract volatile oils from *Cannabis* as this leaves no residue. Although there is limited research on the efficacy of these methods, nontoxic solvents are clearly preferable.

Heavy metals. *Cannabis* has been shown to be especially effective in absorbing metals such as cadmium and copper from contaminated soils.[26] Making matters worse, *Cannabis* is also intentionally contaminated with metals to increase the market weight. In 2008, 150 people in Germany developed lead poisoning as the result of using adulterated cannabis.[27]

Microbial. Indoor growth results in increased susceptibility of *Cannabis* to contamination by microbes such as fungi, bacteria, and plant viruses. Growing and drying also increase the risk of microbial contamination.[28] *Penicillium* species are the predominant microbe contamination in marijuana grown indoor.[29] *Cannabis* has even been shown to be contaminated with human pathogens such as hepatitis A,[30] hepatitis B,[31] and salmonella.[32] Chronic pulmonary aspergillosis has been found in immunocompromised individuals using medicinal marijuana.[33]

Synthetic Cannabinoids

There is limited research on synthetic cannabinoids (SCBs) such as "Spice," "K2," "herbal incense," and others. Toxicity reports include tachycardia, hypertension, tachypnea, chest pain, heart palpitations, hallucinations, racing thoughts, and seizures.[34] The most common clinical signs of toxicity are neurologic including agitation, central nervous system depression/coma, and delirium/toxic psychosis.[35] There have been reports of acute renal failure associated with the use of these synthetic analogues.[36] These compounds appear significantly more toxic than cannabis and should be avoided.[37]

Detoxification

The liver metabolizes THC through hydroxylation and oxidation reactions catalyzed by cytochrome P450 enzymes, especially CYP2C9 and CYP3A4.[38,39,40] Approximately 65% is excreted in the feces and 20% in urine.[41] THC is excreted in the urine primarily as the glucuronic acid conjugate THCCOOH, which has a half-life between 30 and 44 hours.[42]

Clinical Indications of Toxicity

Long-term smoking of marijuana leaf has been shown to cause airway obstruction[43]; squamous metaplasia[44]; impaired psychomotor performance; increased incidence of schizophrenia[45]; cancer of the mouth, jaw, tongue, and lung; and leukemia in children of marijuana smoking mothers.[46] Although marijuana smoke has been shown to contain carcinogenic compounds, research is unclear about whether a link with lung cancer exists.[47]

Population studies in adults show that heavy cannabis use increases the risk of accidents, can produce dependence and has been associated with poor social outcomes and mental health.[48] Long-term daily use has been associated with decreased motivation, impaired ability to learn, and reduced sexual desire.[49,50] Daily heavy inhalation can produce bronchial irritation and may lead to long-term pulmonary damage secondary to the associated hydrocarbon residues.[51]

Intervention

As noted previously, marijuana can be considered a "toxin of choice." This means dosage and toxicity are under the control of the user. Abstinence is, of course, the most effective way to decrease cannabis toxicity. However, for most patients, management to prevent excessive use and education to choose the least toxic forms is more likely. Research has shown little benefit treating cannabis dependence with prescription drugs such as selective serotonin reuptake inhibitor (SSRI) antidepressants, mixed-action antidepressants, atypical antidepressants (bupropion), anxiolytics (buspirone), and norepinephrine reuptake inhibitors.[52]

N-acetyl-cysteine (NAC) at 1200 mg BID has shown benefits because its induction of glutathione synthesis helps mitigate many of the toxic effects and improve the odds of abstinence.[53,54]

Vaporization ("vaping") of extracts appears the preferred method of use as it reduces respiratory exposure to toxic particulates and carcinogens.[55] For those smoking the dried plant (buds, leaf, flowers, etc), the type of filtration significant affects toxic chemical residue. Hand-held glass pipes allow the most toxins, unfiltered water pipes are intermediate, and the lowest quantity is found with filtered water pipes.[56] Heating may make many of contaminants more toxic.[57]

Conclusion

Many of our patients are using, and in some cases abusing, *Cannabis*. Our key clinical responsibility is to help those who choose to use marijuana—for whatever reason—to do so responsibly and as safely as possible. The most common ways of obtaining and using marijuana clearly result in clinical toxicity. Interestingly, most of this toxicity appears to be determined by contaminants and the consumption method.

We need to advise our patients to carefully avoid marijuana which is contaminated with agricultural chemicals, metals, microbes, solvents, etc. In addition, damage can be decreased by recommending the least toxic ways of consuming marijuana. Because the primary psychoactive constituent of marijuana, THC, appears to have little toxicity (though it likely plays a major role in the psychological issues), our guidance should focus on ways to limit exposure to everything else. This suggests recommending organically grown product, CO_2 extraction, and vaporization rather than smoking agricultural chemical-laced dried plant.

In This Issue

Associate Editor Jeffrey Bland, PhD, continues his thoughtful commentaries on how personalization is critical to solving the health care system crisis. I especially like this comment: "We cannot solve the kidney disease problem through the building of more dialysis centers or by providing a greater number of kidney transplants."

Regular columnist John Weeks reminds us of the huge problem of science and policy distortion by the integrative medicine antagonists. Fortunately, there is good news with natural childbirth and home births receiving more recognition. Very sad about the passing of my friend Robert Duggan, MA. We worked together when Hillary Clinton invited us to make recommendations for how to integrate natural medicine into the health care system. He was a visionary who will be sorely missed.

We present the second of the multipart series on probiotics written by master of science nutrition graduates of Elizabeth A. Lipski, PhD: Keren E. Dolan, MS; Heather J. Finley, MS, RD; Cathleen M. Burns, MS, RD; Margaret G. Gasta, MS, RDN; Crystal M. Gossard, MS; Emily C. Parker, MS, RD; Jessica M. Pizano, MS; and Christy B. Williamson, MS. This part focuses on traditional and modern fermented foods—quite a fascinating read and important for providing our patients food choices for probiotics.

Managing editor, Craig Gustafson, interviewed for this issue Ellen Kamhi, PhD, RN. I think her thoughts on how the gut affects the hypothalamic-pituitary-adrenal (HPA) axis are quite intriguing. Especially interesting is her novel use of several botanical medicines to help normalize HPA function. Also, a very thoughtful discussion on stress and sleep. Well worth the read. Wish we had a flow chart to track all the interactions she covered.

I am very excited that Associate editor, David Riley, MD, continues to recruit helpful case reports. Patrick Veerkamp; Nico Mousdicas, MD; and Robert Bednarek, MD, provide us an effective integrative medicine approach to rosacea fulminans. The color pictures are quite convincing.

We do not publish much about integrative medicine education as *IMCJ* focuses on clinical application. Nonetheless, sometimes a submission will catch my attention. In this case, I thought it was useful assessing what works when trying to teach a new class of interventions. Rebecca Boesl, APRN, and Heidi Saarinen, APRN, provide original research on the challenges and successes teaching health care professionals about essential oils.

Associate editor, Bill Benda, MD's "Rider on the Storm" reminds us of how extremism and fear mongering are so damaging—on both sides of whatever aisle people are congregating.

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