

The Highs and Lows of Medical Marijuana

Jill Vargo Cavalet, MHS, PA-C

Marijuana use is prevalent worldwide yet remains controversial in health care. The general public often regards marijuana as a benign substance, but clear risks are associated with its use. Given the legalization of medical marijuana in more than 20 states, clinicians need to be aware of its negative effects—and its potential therapeutic benefits.

Marijuana has been used medicinally worldwide for thousands of years.^{1,2} In the early 1990s, the discovery of cannabinoid receptors in the central and peripheral nervous systems began to propagate interest in other potential therapeutic values of marijuana.³ Since then, marijuana has been used by patients experiencing chemotherapy-induced anorexia, nausea and vomiting, pain, and forms of spasticity. Use among patients with glaucoma and HIV/AIDS has also been widely reported.

In light of this—and of increasing efforts to legalize medical marijuana use across the United States—clinicians should be cognizant of the substance's negative effects, as well as its potential health benefits. Marijuana has significant systemic effects and associated risks of which patients and health care providers should be aware. Questions remain regarding the safety, efficacy, and long-term impact of

use. Use of marijuana for medical purposes requires a careful examination of the risks and benefits.

PHARMACOKINETICS

Marijuana contains approximately 60 cannabinoids, two of which have been specifically identified as primary components. The first, delta-9 tetrahydrocannabinol (THC), is believed to be the most psychoactive.^{4,5} THC was identified in 1964 and is responsible for the well-documented symptoms of euphoria, appetite stimulation, impaired memory and cognition, and analgesia. The THC content in marijuana products varies widely and has increased over time, complicating research on the long-term effects of marijuana use.^{5,6}

The second compound, cannabidiol (CBD), is a serotonin receptor agonist that lacks psychoactive effects. Potential benefits of CBD include antiemetic and anxiolytic properties, as well as anti-inflammatory effects. There is some evidence to suggest that CBD might also have antipsychotic properties.^{1,4}

AVAILABLE FORMULATIONS

Two synthetic forms of THC have been approved by the FDA since 1985 for medicinal use: nabilone (categorized as a Schedule II drug) and dronabinol (Schedule III). Both are cannabinoid receptor agonists approved for treating chemotherapy-induced nausea and vomiting. They are recommended for use after failure of standard therapies, such as 5-HT₃ receptor antagonists, but overall interest has decreased since the advent of agents such as ondansetron.^{2,4}

Jill Vargo Cavalet is a Clinical Associate Professor in the Department of PA Sciences at Saint Francis University in Loretto, PA, and practices clinically in inpatient psychiatry.

QUICK SUMMARY

Recommendations for Marijuana Use

Evidence for

Chemotherapy-associated nausea/vomiting
Glaucoma
Multiple sclerosis spasticity and/or pain

No current evidence for

Alzheimer disease	Parkinson disease
Chron disease	Rheumatoid arthritis
Chronic pain	Seizures
HIV/AIDS	Tourette syndrome
Huntington disease	

Nabiximols, an oral buccal spray, is a combination of THC and CBD. It was approved in Canada in 2005 for pain management in cancer patients and for multiple sclerosis-related pain and spasticity. It is not currently available in the US.^{2,4}

Marijuana use is currently legal in 25 states and the District of Columbia.^{7,8} However, state laws regarding the criteria for medical use are vague and varied. For example, not all states require that clinicians review risks and benefits of marijuana use with patients. Even for those that do, the lack of clinical trials on the safety and efficacy of marijuana make it difficult for clinicians to properly educate themselves and their patients.⁹

LIMITATIONS OF RESEARCH

Why the lack of data? In 1937, a federal tax restricted marijuana prescription in the US, and in 1942, marijuana was removed from the US Pharmacopeia.^{2,4} The Controlled Substances Act in 1970 designated marijuana as a Schedule I drug, a categorization for drugs with high potential for abuse and no currently accepted medical use.⁹ Following this designation, research on marijuana was nearly halted in the US. Several medical organizations have subsequently called for reclassification to Schedule II in order to facilitate scientific research into marijuana's medicinal benefits and risks.

Research is also limited due to the comorbid use of tobacco and other drugs in study subjects, the variation of cannabinoid levels among products, and differences in the route of administration—particularly smoking versus oral or buccal routes.⁵ Conducting marijuana research in a fashion similar to pharmaceuticals would not only serve the medical community but also the legislative faction.

TABLE 1
Effects of Acute Marijuana Intoxication

Anxiety	Increased sociability
Dizziness	Laughter
Dry mouth	Perceptual alterations
Euphoria	Relaxation
Impaired motor function	Talkativeness
Increased appetite	

Sources: Hall and Degenhardt. *Lancet*. 2009⁵; American Psychiatric Association.¹⁰



Credit: iStock.com/thegoodphoto

Despite these obstacles, there is some available evidence on medical use of marijuana. A review of the associated risks and potential uses for the substance follows.

RISKS ASSOCIATED WITH MARIJUANA USE

Acute effects

Most symptoms of marijuana intoxication are attributed to the THC component and occur due to the presence of cannabinoid receptors in the central nervous system (see Table 1).^{5,10} Additional objective signs of acute or chronic intoxication include conjunctival injection, tachycardia, cannabis odor, yellowing of fingertips (from smoking), cough, and food cravings.¹⁰

A more recently identified effect of long-term marijuana use is a paradoxical hyperemesis syndrome, in which individuals experience nausea, vomiting, and abdominal pain. They obtain relief with hot showers or baths.^{6,8}

Since there is a near absence of cannabinoid receptors in the brain stem, marijuana does not stimulate the autonomic nervous system. It is therefore believed that marijuana use cannot be fatal. Corroborating this theory, no deaths have been reported from marijuana overdose.^{2,11}

Withdrawal symptoms

Approximately 10% of regular marijuana users become physically and psychologically dependent on the substance. Once tolerance develops, withdrawal symptoms occur with cessation of use (see Table 2, page 42).^{2,5,10} Symptoms peak within the first week

TABLE 2

Symptoms of Marijuana Withdrawal

Abdominal pain	Diaphoresis
Anger or aggression	Fever
Anorexia or weight loss	Headache
Anxiety	Insomnia
Chills	Irritability
Craving	Restlessness
Depression	Tremors

Sources: Bostwick. *Mayo Clin Proc.* 2012³; Hall and Degenhardt. *Lancet.* 2009⁵; American Psychiatric Association.¹⁰

following cessation and may last up to two weeks. Sleep disturbances may occur for more than one month.¹⁰

Unlike with other substances of abuse, there are no pharmaceutical agents to treat marijuana withdrawal; rather, treatment is supportive. Marijuana users often resume use following a period of cessation in order to avoid withdrawal.

Chronic effects

Dental/oral. Smoking marijuana is associated with an increased risk for dental caries, periodontal disease, and oral infections.¹ Premalignant oral lesions, such as leukoplakia and erythroplakia, have also been reported. Patient education on the risks and need for proper oral hygiene is vital, as are regular dental examinations.

Respiratory. There are several known pulmonary implications of smoking marijuana, and therefore, this route of administration is not recommended for medicinal use. Respiratory effects of marijuana smoke are similar to those seen with tobacco: cough, dyspnea, sputum production, wheezing, bronchitis, pharyngitis, and hoarseness.⁴ Increased rates of pneumonia and other respiratory infections have also been identified.⁶ Research on long-term marijuana smoking has revealed hyperinflation and airway resistance.⁶ At this time, evidence is inconclusive as to whether smoking marijuana leads to chronic obstructive pulmonary disease.¹

Studies have compared the chemical content of tobacco and marijuana and found similar components, including carcinogens, but data regarding concentrations of these chemicals are conflicting.^{1,4} It is unknown whether vaping (a trending practice in which a device is used to heat the substance prior to inhalation) reduces this risk.⁴

Unfortunately, data regarding the carcinogenic

effects of long-term marijuana smoking are inconclusive; some studies have shown potential protective effects.⁴⁻⁶ Other evidence suggests that the risk is lower in comparison to tobacco smoking.⁶

Cardiovascular. The effects of marijuana on the cardiovascular system are not fully understood. Known symptoms include tachycardia, peripheral vasodilation, hypotension, and syncope.⁴ There is some evidence that marijuana use carries an increased risk for angina in patients with previously established heart disease.⁵ Patients, especially those with known cardiovascular disease, should be educated about these risks.

Reproductive. There are several identified reproductive consequences of marijuana use. Research has found decreased sperm count and gynecomastia in men and impaired ovulation in women.⁴ Studies on marijuana use in pregnancy consistently reveal low birth weight—this effect is, however, less than that seen with tobacco smoking.⁵ Other complications or developmental abnormalities may occur, but there is currently a lack of evidence to support further conclusions.

Neurologic. The use of marijuana results in short-term memory loss and other cognitive impairments. There is conflicting evidence as to whether long-term effects remain after cessation.^{5,6} Because acute intoxication impairs motor skills, it is associated with increased rates of motor vehicle accidents.⁶ Driving while under the influence of marijuana should be cautioned against.

Psychiatric. Marijuana use is associated with the onset and exacerbation of acute psychosis. However, its role as a causal factor in schizophrenia has not been established.^{4,10} There is some evidence to suggest that CBD has antipsychotic properties, warranting further research. An amotivational syndrome has also been affiliated with chronic marijuana use; affected individuals exhibit a lack of goal-directed behavior, which may result in work or school dysfunction.¹⁰ Several studies have supported an association between marijuana use and risk for depression and anxiety. Due to the extensive risk factors for these disorders, including genetic and environmental, causality has yet to be established.^{5,6}

CONDITIONS FOR WHICH MARIJUANA MAY OFFER THERAPEUTIC BENEFITS**Glaucoma**

Research has demonstrated that marijuana decreases intraocular pressure, and many patients with

glaucoma use marijuana. However, it is not recommended as firstline treatment.

The beneficial effects of smoked marijuana are short-lived, requiring patients to dose repeatedly throughout the day. Use is also often discontinued due to adverse effects including dry mouth, dizziness, confusion, and anxiety.⁸

Topical preparations of THC have not been successfully developed due to the low water solubility of cannabis and minimal penetration through the cornea to the intraocular space.⁸ Standard treatments available for glaucoma are more effective and without obvious psychoactive effects.⁶

Nausea

One of the first medical uses of marijuana was for nausea. Due to the presence of cannabinoid receptors that govern food intake, marijuana is known to stimulate appetite, making its use in reducing chemotherapy-associated nausea and vomiting widespread.^{2,6} Despite the variation in state laws regarding medical use of marijuana, cancer is included as a qualifying illness in every state that allows it.⁸ Cannabis-based medications may be useful for treating refractory nausea secondary to chemotherapy; however, dronabinol and nabilone are not recommended as firstline therapies.¹²

HIV/AIDS

Short-term evidence suggests that patients with HIV and/or AIDS benefit from marijuana use through improved appetite, weight gain, lessened pain, and improved quality of life.^{6,13} Studies with small sample sizes have been conducted using smoked marijuana and dronabinol.⁸ Long-term studies are needed to compare the use of marijuana with other nutritional and caloric supplements. Overall, reliable research regarding the therapeutic value of marijuana in these patients is inconclusive, and therefore no recommendations for incorporating marijuana into the treatment regimen have been made.⁸

Multiple sclerosis

For centuries, marijuana has been used for pain relief. The discovery of cannabinoid receptors in high concentrations throughout pain pathways of the brain supports the notion that marijuana plays a role in analgesia. While response to acute pain is poor, there is evidence to suggest that various cannabis formulations relieve chronic neuropathic pain and spasticity, as seen in multiple sclerosis.^{3,6}

Subjective improvements in pain and spasticity were seen with the use of oral cannabis extract, THC, and nabiximols.¹¹ Smoked marijuana is of uncertain efficacy and is not recommended for use in this patient population; it has been shown to potentially worsen cognition.^{8,11}

Seizures

Research into the role of marijuana in decreasing seizure frequency is inconclusive.¹¹ Large studies with human subjects are lacking, and most data thus far have come from animals and case studies.⁸ Some case reports have suggested a decrease in seizures with marijuana use, but further investigation is needed.⁶

At this time, it is not appropriate to recommend marijuana for patients with seizure disorders, but the use of cannabidiol might be more promising. Studies are ongoing.¹⁴

Alzheimer disease

Alzheimer disease is the most common cause of dementia.⁸ Despite known adverse effects on memory and cognition with acute use, studies have shown that marijuana might inhibit the development of amyloid beta plaques in Alzheimer disease.⁴ Further research on dronabinol has not provided sufficient data to support its use, and no studies utilizing smoked marijuana have been performed.⁸ Therefore, no recommendations exist for the use of marijuana in this patient population, and further research is warranted.

Ongoing research

There are some additional areas of potential therapeutic use of marijuana. Limited evidence has revealed that marijuana has anti-inflammatory properties, leading researchers to examine its use for autoimmune diseases, such as rheumatoid arthritis and Crohn disease. Studies investigating marijuana's potential ability to inhibit cancer growth and metastasis are ongoing.

Unfortunately, research in patients with Parkinson disease has not shown improvement in dyskinesias.¹¹ Studies on other movement disorders, such as Tourette syndrome and Huntington disease, have not shown symptom improvement with marijuana use. Research on these conditions and others is ongoing.

CONCLUSION

Marijuana use has negative effects on a variety of body systems, but it also may provide therapeutic

continued on page 53 >>

>> continued from page 44

benefit in certain patient populations. Clinicians and patients are currently hampered by the dearth of reliable information on its safety and efficacy (resulting from federal restrictions and other factors). Comparative studies between marijuana and established standards of care are needed, as is additional research to identify therapeutic effects that could be maximized and ways to minimize or eliminate negative sequelae. **CR**

REFERENCES

1. Greydanus DE, Hawver EK, Greydanus MM, Merrick J. Cannabis: effective and safe analgesic? *J Pain Manage*. 2014;7(3):209-233.
2. Bostwick JM. Blurred boundaries: the therapeutics and politics of medical marijuana. *Mayo Clin Proc*. 2012;87(2):172-186.
3. Karst M, Wippermann S, Ahrens J. Role of cannabinoids in the treatment of pain and (painful) spasticity. *Drugs*. 2010;70(18):2409-2438.
4. Owen KP, Sutter ME, Albertson TE. Marijuana: respiratory tract effects. *Clin Rev Allergy Immunol*. 2014;46(1):65-81.
5. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009;374(9698):1383-1391.
6. Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370(23):2219-2227.
7. National Conference of State Legislatures. State medical marijuana laws (updated 7/20/2016). www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Accessed September 7, 2016.
8. Belendiuk KA, Baldini LL, Bonn-Miller MO. Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders. *Addict Sci Clin Pract*. 2015;10(1):1-10.
9. Hoffmann DE, Weber E. Medical marijuana and the law. *N Engl J Med*. 2010;362(16):1453-1457.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
11. Koppel B, Brust J, Fife T, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders. *Neurology*. 2014;82(17):1556-1563.
12. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database Syst Rev*. 2015;(11):CD009464.
13. Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database Syst Rev*. 2013;(4):CD005175.
14. Gloss D, Vickrey B. Cannabinoids for epilepsy. *Cochrane Database Syst Rev*. 2012;(6):CD009270.