Pharmacy and Wellness Review

Volume 6 | Issue 1 Article 2

August 2014

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Marijuana and Its Cardiovascular Implications

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-14-215-H04-P

Objectives

After completion of this program, the reader should be able to:

1. Know the prevalence of recreational and medicinal marijuana use.
2. Identify characteristics that align with the potential for marijuana abuse.
3. Understand the pharmacological effects of marijuana on the heart.
4. Recognize the risks and damages to the cardiovascular system from marijuana use.
5. Summarize the pharmacist's role in counseling over marijuana use.

Abstract

As marijuana becomes legalized for medical use, it is important for prescribers and pharmacists to be knowledgeable about the important aspects of marijuana such as mechanism of action, indications and abuse potential. Although marijuana's medicinal benefits are frequently reported, the risks, namely cardiovascular risks, associated with its utilization are often overlooked. Use of marijuana has been reported to increase the risk of myocardial infarction, tachycardia and hypotension, among others. Health care providers must determine if marijuana's benefits outweigh such risks when marijuana therapy is an option. It is also important for pharmacists to understand how to successfully counsel patients using medical marijuana so that the patient has an effective course of therapy.

Key Terms

Cannabinoids; Cannabis; Cardiovascular Diseases; Food and Drug Administration (U.S.); Humans; Hypotension; Medical Marijuana; Myocardial Infarction; Pharmacists; Review Literature; Risk; Risk Factors; Tachycardia

Introduction

The utilization of medicinal marijuana has been commonplace since the earliest of civilizations. Most of marijuana's positive medicinal qualities are noted because of this long period of use. However, due to the criminalization of marijuana, the determination of marijuana's negative qualities has lagged behind. Because of marijuana's resurgence and shifting public opinion, identifying possible negative effects is an important consideration when discussing marijuana as a treatment option.

Medicinal marijuana dates back centuries to the year 2737 B.C.E. when it was first recorded by the Chinese Emperor, Shen Neng, that Cannabis tea was effective for use in the treatment of gout, malaria, beriberi, rheumatism and poor memory.[1] Centuries later, the founder of surgery, Hua T'o, used a Cannabis tincture as an anesthetic in patients.

In more recent times, the Ohio State Medical Society recognized the potential uses of medicinal Cannabis in 1860 C.E., noting that it was especially useful in treating pain, inflammation and cough.[1] Even the 1868 edition of the United States Dispensatory listed Cannabis tinctures for indications such as decreased appetite, decreased sexual interest, mental illnesses, gout, cholera, hydrophobia and insomnia. Cannabis containing products were popular enough that the Squibb Company released a morphine and Cannabis product named "Chlorodyne." Eli Lilly and Parke-Davis also manufactured Cannabis containing products to be used as antispasmodics, sedatives and analgesics. At the conclusion of the Mexican-American War, Mexican migrants introduced recreational use of marijuana to the United States. However, instead of promoting marijuana usage, the Great Depression created many irrational xenophobic sentiments causing a fear of the "Marijuana Menace."[2] The decreased popularity of marijuana allowed the Marijuana Tax Act of 1937 to be passed, which put a burdensome tax on marijuana sales and significantly reduced production of Cannabis containing compounds. Eventually in the 1950s, the Boggs Act and Narcotic Control Act made marijuana possession and distribution a federal offense.[1] Despite marijuana's criminalization, it remains an extremely popular recreational drug as well as medicinal agent.

Throughout the last five decades, researchers have been investigating what gives marijuana its medicinal and hallucinogenic properties. In 1967, Mechoulam and Gaoni successfully identified and synthesized the main psychoactive ingredient in marijuana, (−)-trans-Δ9-tetrahydrocannabinol (THC).[3] It was not until 1990 that Matsuda et al. were able to identify and genetically sequence the endogenous cannabinoid receptors. They found that these receptors, which comprise the endocannabinoid system, are highly concentrated in the brain. They are known as CB_1 receptors. Soon thereafter, a second type of cannabinoid receptor was discovered in the periphery and the immune system and was named the CB_2 receptor. Since that time, medications that utilize the endo-

cannabinoid system have been an area of great interest. There are currently two U.S. Food and Drug Administration (FDA) approved medications that partially agonize the endocannabinoid system: dronabinol (synthetic THC) and nabilone (synthetic cannabinoid).[4] These are used in patients experiencing nausea, vomiting and loss of appetite.

Indications

Marijuana is currently prescribed for pain secondary to cancer, neuralgia, headaches and glaucoma.[5] It is also used to reduce muscle spasms in patients suffering from multiple sclerosis. Cancer and human immunodeficiency virus patients often use marijuana therapy to suppress nausea and induce an appetite, which decreases weight loss. Additionally, marijuana has been found to alleviate irritable bowel symptoms associated with Crohn's disease. Finally, marijuana can be used to reduce seizures in epileptic patients.

Epidemiology

There are approximately 200 million marijuana users in the world. This is approximately 4 percent of the worldwide adult population.[6,7] The highest percentage of marijuana users are located in Australia followed by North America.[7] Approximately 40 percent of the North American population that uses marijuana for a lifetime are 12 years and older while 60 percent were nonusers or occasional users. As of November 2014, Oregon and the District of Columbia were the most recent areas to legalize recreational marijuana. However, there are still legalization issues surrounding the District of Columbia due to it being a district and not a state. Recreational marijuana is now legalized in a total of four states: Alaska, Colorado, Washington and Oregon.[6,8] In comparison, medicinal marijuana use is legal in 23 states, making medicinal marijuana use more prevalent than some people realize.[9]

There are more males who use medicinal marijuana than females; more than 75 percent are males while the remaining 25 percent are females, as indicated by Figure 1.[10] The average age of males who use medicinal marijuana is 31 years while average age of females who use medical marijuana is 36 years. When the medicinal marijuana users were divided based on race, the highest percentage of users were Caucasian followed by African American, Hispanic, Asian and other. Almost 69 percent of the medicinal marijuana users were Caucasian, which is shown in Figure 2. Although the prevalence of Asian and Hispanic users is lower than Caucasian, younger users were more likely to be Asian or Hispanic. When evaluating education levels, nearly half of the users had a high school diploma. In descending order following the high school degree, medicinal marijuana users were those who had a bachelor's degree, did not complete high school, had an associate's degree, had a master's degree, and had a doctorate, which is indicated by Figure 3. In summary, the average medicinal marijuana user could be a Caucasian male who has finished high school.

Figure 1. Prevalence of medicinal marijuana users based on sex.[10]

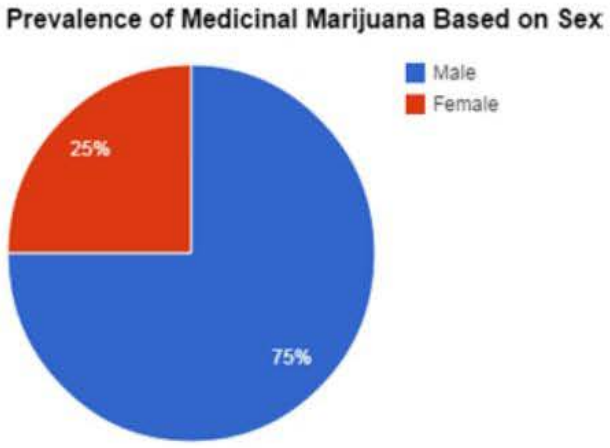


Figure 2. Prevalence of medicinal marijuana users based on race.[10]

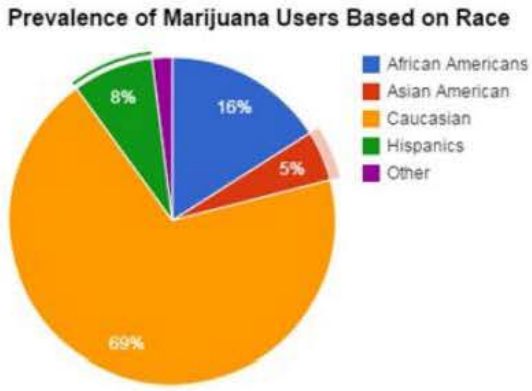
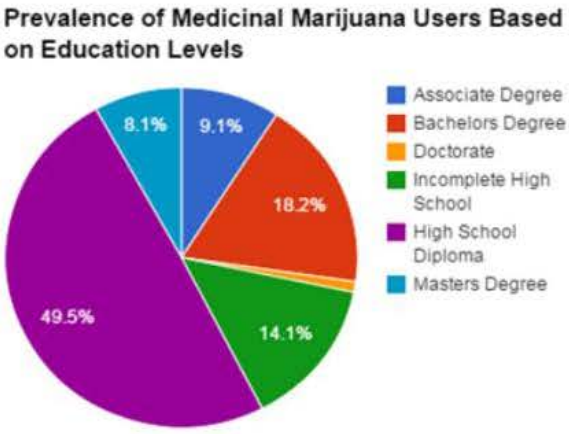


Figure 3. Prevalence of medicinal marijuana users based on education level.[10]



Potential Abuse

Of the 200 million marijuana users, approximately one in 10 users will become dependent on Cannabis.[7] Just like narcotics and other drugs, the risk of becoming dependent on Cannabis increases when it is used more frequently. Fifty percent of daily users of marijuana will become dependent users. Some of the potential causes of marijuana use disorder

include genetics, environmental influences and use of other drugs.[7,11] Studies have suggested there are three genes possibly associated with Cannabis use disorder, which are C17orf58, BPTF and PPM1D.[12] As for environmental influences, disruptive homes and users who had first-degree relatives that are abusers are 5.8 times more likely to abuse as well.[13] Over the years, Cannabis has become easier to obtain, which has increased the chance of users abusing marijuana.[14] There are over 13 million people who depend on Cannabis.[15] Cannabis dependence is more likely to occur in younger people such as adolescents.[7] The most common profile of someone who abuses marijuana is a male between the ages of 20 and 24 years who lives in a high income region.

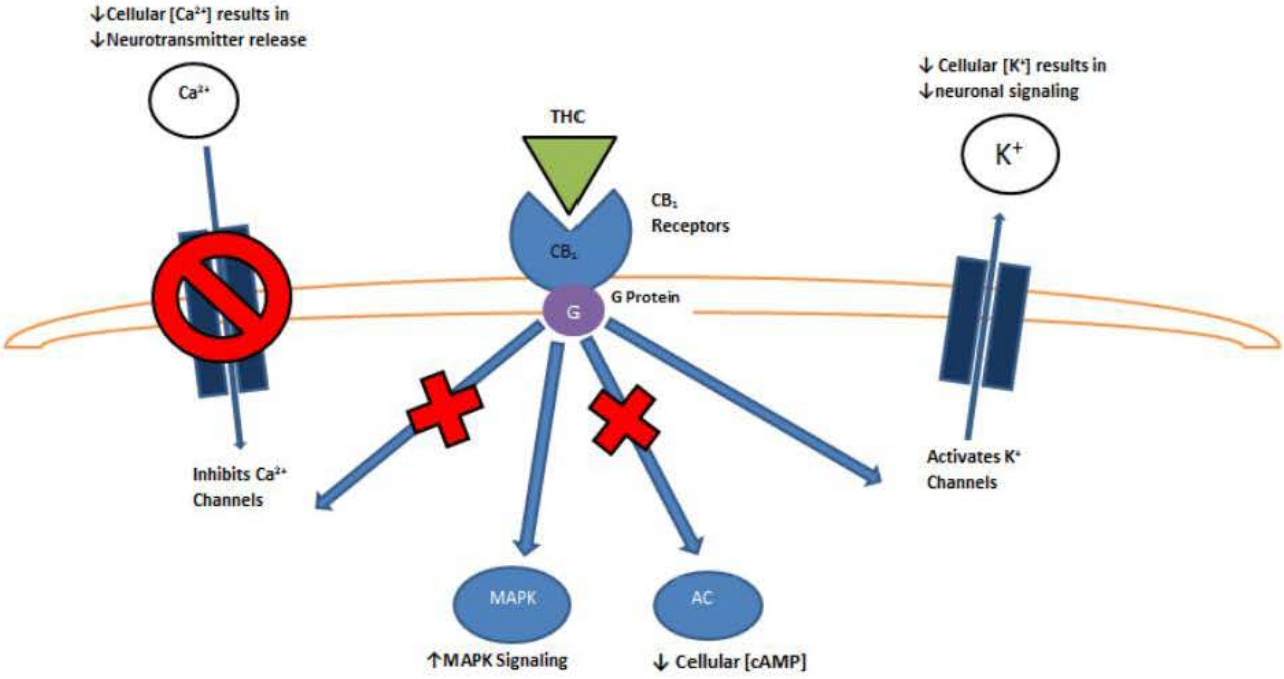
Pharmacology

Marijuana's active chemical, THC, binds to CB_1 receptors, which are G protein coupled.[16] These receptors are located on the neuronal surface, acting as a partial agonist of the endocannabinoid system. This activates a G_i protein causing the α-subunit to dissociate from the βγ-subunit, which will inhibit the activation of adenylate cyclase (AC) while activating the mitogen activated protein kinase (MAP). Inhibiting AC decreases the levels of intracellular cyclic adenosine monophosphate (cAMP). With decreased levels of cAMP, cAMP-dependent protein kinase A (PKA) will not be activated. Furthermore, without active PKA, outward rectifying potassium channels are not as highly phosphorylated, allowing potassium to exit the cell, leading to decreased neuronal signaling. Mitogen activated protein kinase, however, leads to cellular growth. N-type and P/Q-type calcium channels are also inhibited. This reduces the intracellular calcium concentration, resulting in a decreased release of neurotransmitters such as glutamate, gamma aminobutyric acid (GABA), norepinephrine, dopamine, serotonin and acetylcholine.[16,17] This process is illustrated in Figure 4.

Systemically, acute administration of THC causes sinus tachycardia by sympathetic stimulation, leading to increased sinus node automaticity.[18] Sympathetic stimulation causes the release of acetylcholine, which activates nicotinic receptors in the post ganglionic neurons. This stimulates the release of norepinephrine, which binds to β-1 receptors of the heart resulting in positive chronotropic and inotropic cardiac effects. Increased cardiac output occurs secondary to the increased heart rate and peripheral vasodilation from sympathetic activation. This increases sympathetic tone and decreases parasympathetic tone. The increased heart rate causes a shortened pre-ejection period while prolonging left ventricular ejection time with no difference in afterload, suggesting cardiologic improvement. However, there are parameters negatively affected by marijuana usage. Supine tachycardia and increased blood pressure are noted, with hypotension occurring in the upright position.[19]

When marijuana is smoked, the bioavailability of THC is between 2 and 56 percent, reaching peak plasma concentrations nine minutes after the first inhalation.[20] Psychoactive effects begin almost instantly and reach their peak two to three hours later. Effects can last between four and 12 hours depending on the dose and user.[21] Marijuana is rapidly absorbed through the lungs and is distributed to highly perfused tissues such as the lung, heart, brain and liver. This is due to THC's highly lipophilic properties. Tissue concentrations reach their peak four to five days after use and have an elimination half-life of seven days.[22] The THC is metabolized mainly through the cytochrome P450 (CYP450) system of the

Figure 4. Summary of THC's effects.[16,17]



liver, with metabolites detectable as early as 13 minutes after the initial inhalation of marijuana.[20] After five days, 80 to 90 percent of THC is excreted either in the feces (65%) or in the urine (20%). The THC urine concentration detection window varies by frequency of utilization. A first time marijuana user can test negatively for THC a few hours after smoking, but a chronic user can test positively for THC up to 67 days from the time of marijuana use.

Risks/Damages to the Cardiovascular System

Although medicinal marijuana is beneficial to some, there are many negative consequences related to medicinal marijuana use. There are known cardiovascular issues related to the use of marijuana. For instance, users are 4.8 times more likely to experience a myocardial infarction within one hour of using marijuana.[6] Those who do experience a myocardial infarction while using marijuana have a higher mortality rate compared to a person who does not use marijuana. In general, patients who use marijuana more than once per week are at a 4.3 times higher risk for mortality. Marijuana use also increases the risk of ischemic stroke. Due to decreased oxygen delivery from smoking, users have a higher oxygen demand. Patients who do use marijuana recreationally or medicinally should be aware of an increased risk for cardiovascular events. There is a lot of interest in determining how this cardiovascular damage occurs.

Due to the ethical and moral issues concerning marijuana, there are a limited number of controlled studies that definitively explain a correlation between independent variables (marijuana use versus mortality/cardiovascular stress). The majority of the cases discussed are individual events that have been reported throughout the United States. Although statistical significance of a cause-and-effect relationship cannot be achieved without comparison to other subjects, these cases give insight to what patient outcomes can occur.

The majority of patients studied after marijuana use either had healthy coronary arteries or minimal coronary irregularities. A reported case of a 34-year-old man showed a right bundle-branch-type ventricular tachycardia precipitated by slow coronary blood flow.[23] Upon admission to the emergency department (ED), the patient presented with palpitations, shortness of breath (SOB), chest pain and near syncope from working in his garden. He also claimed a three month history of occasional "heart fluttering" with dizziness. The patient admitted to tobacco use (<½ pack a day) and marijuana use (twice daily). Coronary angiogram indicated healthy vessels with no stenosis; however, coronary blood flow was markedly reduced (flow grade of 1 to 2) according to the thrombolysis in myocardial infarction (TIMI) classification. Coronary blood flow was relatively antegrade beyond an occlusion with some filling of the distal coronary bed. Coronary flow was normalized after administration of verapamil and cessation of marijuana. Ventricular tachycardia was no longer inducible in the electrophysiology laboratory. This case suggests that marijuana could precipitate some abnormalities in coronary microcirculation that could potentially lead to ventricular tachycardia.

Myocardial infarctions (MI), specifically ST-elevated myocardial infarctions (STEMI), have also been reported after the use of marijuana. A 37-year-old obese man presented to the ED with chest pain and increased perspiration immediately after marijuana use.[24] The patient denied any family history of coronary disease and diabetes. The patient also denied SOB, syncope, dizziness and palpitations. The patient used Viagra 100mg approximately 36 hours before the onset of pain. The patient's hypertension was controlled with Norvasc 5mg daily. The patient presented with an unremarkable blood pressure (BP) and heart rate. Electrocardiogram (EKG) results showed a STEMI as evidenced by an elevated ST segment and increased creatinine kinase-MB fraction and troponin levels. After percutaneous intervention, the patient was discharged home with a normal ejection fraction per echocardiogram. In this study, marijuana effects to the heart were amplified due to Viagra's CYP3A4 inhibition. Without CYP3A4 metabolism of marijuana, the active chemical led to coronary vasospasms regardless of previously healthy coronaries.

To assess the long-term mortality associated with marijuana use, a multicenter inception cohort study was conducted.[25,26] The study was titled "The Determinants of MI Onset." Three thousand eight hundred eighty-eight patients were evaluated from 1989 to 1996 and followed up for mortality via the National Death Index. After such time, 519 patients died, including 22 of 109 reporting marijuana use before their MI. No statistical significance was established for the association between marijuana use and mortality. However, reported users of marijuana had a mortality rate 29 percent higher (95% confidence interval (CI) 0.81-2.05, P=0.28) than nonusers. Also, the rate of MI is 4.8 times greater in the hour after marijuana use compared with other times (95% CI 2.4-9.5). Thus, smoking marijuana is possibly a trigger of acute MI.

Atrial fibrillation (AF) has been recorded in a systematic review of six patients.[27] All patients, age 24.5 ± 7.8 years, experienced AF shortly after marijuana use. In three of the patients, sinus rhythm was recovered via pharmacological therapy. One patient experienced palpitations identified as sinus tachycardia. Two of the patients had loss of consciousness (one of them fell) as marijuana suppresses the central nervous system (CNS) and induces postural hypotension. Only one had hypertension as a comorbidity. All patients had favorable outcomes as AF subsided with marijuana cessation.

So far, there have been no reported cases of short-term or long-term use of Cannabis causing congestive heart failure (CHF).

In these studies discussed, comorbidities (e.g., hypertension) and lifestyle habits (e.g., tobacco use/alcohol consumption) were confounding factors that could have contributed to the aforementioned cardiovascular events. Because these factors' impact on cardiovascular function was not taken into account, it seems that marijuana cannot be the sole contributor. Further controlled trials need to be conducted to clarify marijuana's effect on the heart.

Currently, there are two FDA approved agents on the market that contain THC. Dronabinol (Marinol®) is primarily used to treat chemotherapy-associated nausea and acquired immune deficiency syndrome (AIDS)-related anorexia. Tachycardia, heart palpitations and facial flushing have been reported in 1 percent or more of these patients taking dronabinol in placebo-controlled trials.[28] Nabilone (Cesamet®) contains a synthetic cannabinoid similar to THC and is used for the same purpose. Tachycardia and orthostatic hypotension have been reported in these patients (<1% and 8%, respectively).

Pharmacist's Role

As health care providers, pharmacists can play a key role in counseling and advising patients who are using marijuana. First and foremost, pharmacists must comply with all local, state and federal laws regarding the use of medical marijuana while adhering to the stricter laws. Marijuana remains a schedule 1 substance in all states and infractions of the law can result in strong disciplinary measures from the state licensing board.[29] Some states are suggesting that pharmacies dispense marijuana. If that is the case, all relevant procedures and protocols should be followed in terms of dispensing and identifying possible diversion.[30] Pharmacists should work closely with primary care physicians to ensure marijuana is the most appropriate and effective therapy available and to ensure drug-drug and drug-disease interactions are screened.[29] Drugs that have interactions with THC include barbiturates, sedatives, benzodiazepines, theophylline, disulfiram, fluoxetine and warfarin. Conditions that can be exacerbated with THC include chronic obstructive pulmonary disorder (COPD), hepatitis C, heart disease, stroke or hypertension. If there is a potential interaction or a safer alternative therapy available, pharmacists should use their professional judgment.[31] In terms of counseling, the benefits and risks should be voiced to the patient including potential side effects. After a comprehensive social and medical history is obtained, pharmacists should look for signs of dependence or addiction such as insomnia, increased appetite, sweats, chills and possible hallucinations. Pharmacists should also be able to explain the biological fundamentals of addiction: decreased levels of dopamine in the limbic system translates to decreased feelings of reward. This should include strategies to correct medical withdrawals and helping to prevent relapse.[29] Patients on medical marijuana treatment should be advised to strictly adhere to the therapeutic regimen. Overuse could lead to dependence, withdrawal and, eventually, addiction. If addiction occurs, patients should seek medical attention to initiate marijuana cessation and possible counseling or psychotherapy. There are many local and national addiction lifelines and websites available for patients such as www.lifelineintervention.com. Patients can also call 1-844-238-3665 for help with addiction.

Pharmacists should be able to retrieve and evaluate drug literature and clinical trials to answer completely and accurately any questions that patients may have.[29] Patients that use medical marijuana should be closely supervised during the course of therapy to ensure that compliance is maintained. However, marijuana is still illegal in most states, and pharmacists should not advise patients on how to obtain marijuana. Lastly, pharmacists on Pharmacy and Therapeutics (P&T) committees are key players in the proper dispensing of marijuana. Dispensing entities may rely on these committees for guidance on the proper regulations and dispensing of THC products.

Conclusion

In conclusion, Cannabis has been used medicinally since 2737 B.C.E. The use of marijuana has increased and will continue to increase as its medicinal use becomes legalized in more states. Pharmacists should be aware of Cannabis dependence, which can be caused by various genetic and environmental factors. Pharmacologically, marijuana mediates its effects through CB_1 receptors in the heart and induces the aforementioned cardiac events. There are not enough studies to conclude that cardiac issues are caused by marijuana. However, there is some indication that marijuana can produce detrimental cardiovascular outcomes such as myocardial infarction and atrial fibrillation. Pharmacists can directly impact the lives of those who use marijuana by explaining how it affects the human body, discussing possible adverse reactions and educating on the potential for abuse.

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The authors have no conflict of interest or funding support to disclose.

Assessment Questions

1. The main psychoactive ingredient in marijuana is:
   A. (−)-trans-Δ9-tetrahydrocannabinol
   B. Anandamide
   C. Nabilone
   D. Cannabidiol

2. Medical marijuana use is indicated for:
   A. Pain
   B. Crohn's disease
   C. Epilepsy
   D. All of the above

3. True or False: THC is excreted through the feces only.
   A. True
   B. False

4. What is the most likely profile of a medicinal marijuana user?
   A. Caucasian female with a high school degree
   B. Hispanic male with master's degree
   C. Caucasian male with a high school degree
   D. Asian male with a bachelor's degree

5. True or False: Recreational marijuana is legal in 23 states.
   A. True
   B. False

6. What is the cause of marijuana use disorder?
   A. Genetics
   B. Use of other drugs
   C. Disruptive homes
   D. All of the above

7. True or False: There is sufficient clinical data to definitively show a correlation between marijuana and cardiovascular disease
   A. True
   B. False

8. Marijuana has NOT been shown to precipitate which of the following cardiovascular events?
   A. Reduced coronary flow
   B. Atrial fibrillation
   C. Congestive heart failure
   D. Myocardial infarction

9. Viagra is an ___of the ___ enzyme which can ___ the levels of marijuana.
   A. inducer, CYP3A4, increase
   B. inhibitor, CYP2C19, decrease
   C. inducer, CYP2C19, increase
   D. inhibitor, CYP3A4, increase

10. True or False: Comorbidities (e.g., diabetes, hypertension) are NOT contributing factors to cardiovascular events
    A. True
    B. False

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Pharmacy License #:	**State:**	**ONU Alumni?**	**Y N**

Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	**1**	**2**	**3**	**4**	**5**
The program met the stated goals and objectives:					
Know the prevalence of recreational and medicinal marijuana use.	**1**	**2**	**3**	**4**	**5**
Identify characteristics that align with the potential for marijuana abuse.	**1**	**2**	**3**	**4**	**5**
Understand the pharmacological effects of marijuana on the heart.	**1**	**2**	**3**	**4**	**5**
Recognize the risks and damages to the cardiovascular system from marijuana use.	**1**	**2**	**3**	**4**	**5**
Summarize the pharmacist's role in counseling over marijuana use.	**1**	**2**	**3**	**4**	**5**
The program met your educational needs.	**1**	**2**	**3**	**4**	**5**
Content of the program was interesting.	**1**	**2**	**3**	**4**	**5**
Material presented was relevant to my practice.	**1**	**2**	**3**	**4**	**5**

Comments/Suggestions for future programs:

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Thank you!
Answers to Assessment Questions—Please Circle Your Answer

1. A B C D	**4. A B C D**	**7. A B**	**10. A B**
2. A B C D	**5. A B**	**8. A B C D**	
3. A B	**6. A B C D**	**9. A B C D**	

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is eligible for credit until 12/18/2017.