

Medical Marijuana – Pharmacology and Clinical Effects

Self-Learning Module

PURPOSE

This Self-Learning Module has been developed for EMS provider training. The intent is to provide consistent and concise information to all providers. The content of the Module has been reviewed by the Protocol Development and Review Sub-Committee, and, where applicable, includes the specific standing order, resource and reference material, and instructions for completing the Self-Learning Module to obtain continuing education credit. One hour of SAEMS continuing education credit may be issued following successful completion of the module.

OBJECTIVES

Upon completion of this learning module, the participant will be able to:

1. Know the two primary compounds derived from marijuana
2. Know the routes of administration and their relative differences in time of onset, duration, etc
3. List the clinical effects of medical marijuana and know how these are used for the indications approved in Arizona

INSTRUCTIONS

1. Review the accompanying information, and any additional reference material as necessary.
2. Complete the attached posttest and return it to your supervisor or base hospital manager for continuing education credit.

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History

Cannabis sativa and *cannabis indica* are the botanical names for the two most common plants from which medicinal cannabis, or medical marijuana, is obtained.¹ The cultivation of *cannabis sativa* can be traced as far back as 4000 B.C. There is evidence that fibers from the stems were used in China to manufacture strings, ropes, paper, and textiles. It was also used as a medicine as early as 2700 B.C. for such ailments as constipation, malaria, rheumatic pain, and 'disorders of the female reproductive system'. It was during this time that the first recorded use of the plants psychoactive properties was described. It was written: *...ma-fen (the fruit of cannabis)... if taken in excess will produce visions of devils ... over a long term, it makes one communicate with spirits and lightens one's body...*² Its use spread East and today it is the most used illicit drug in the world.³

Marijuana is the name given to the mixture of leaves and flowers of the plant *C. sativa*. This mixture is usually smoked and upon pyrolysis, the active components are released and absorbed into the bloodstream. Hashish is the name given to the pressed resin gathered from the flower and resin glands. Hashish oil is further derived from the pressed resin and contains the most concentrated amount of the active components.⁴

Pharmacology

C. sativa contains over 545 different chemical compounds of which 104 are termed Cannabinoids.⁵ This term encompasses both naturally occurring and synthetic compounds that bind to cannabinoid receptors. The two major, medically important cannabinoids are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD).⁶ THC is the major mood-altering component responsible for the characteristic 'high' described by users of marijuana.⁷ CBD is non-psychoactive and has anti-inflammatory, anti-oxidant, and anti-emetic effects.⁸ It may also modify the effects of THC via inhibition of cytochrome P450 in the liver.

The mechanism of action of cannabis is mediated through binding to the cannabinoid receptors, CB₁ and CB₂. They act to sense signals outside of the cell and initiate second messenger signaling pathways to effect a response. The CB₁ receptor is one of the most abundant in the brain and is involved in a variety of signaling pathways.⁴ High densities of these receptors are found in the central nervous system (CNS), most notably in the basal ganglia, cerebellum, hippocampus, neocortex, hypothalamus, and

limbic system. The CB₂ receptor is found primarily in the periphery and research is ongoing into its role as a therapeutic target.

As a botanical product, the actual and relative concentrations of cannabinoids varies and is dependent upon multiple factors such as cultivation methods, growing conditions, and preparation. This is especially true of marijuana as it is comprised of the plant material, which has undergone little to no processing. Non-pharmaceutical grade medical marijuana is also subject to inconsistency as these products are not regulated by the Food and Drug Administration. Thus, there is wide variation between samples and difficulty in predicting individual effects. This is in contradistinction to pharmaceutical grade cannabinoids such as Marinol® and Sativex®, which are regulated and have consistent amounts of active cannabinoid. While cannabinoid concentrations are unreliable on an individual basis, analysis of samples confiscated by law enforcement shows that the average content of THC has been increasing over time. In one study, samples had an average THC concentration of 3.4% in 1993 and rose to an average of 8.8% in 2008.⁹

Routes of administration

The two main routes by which cannabis can enter the body are inhalation and ingestion. Inhalation via smoking or vaporization is the most rapid and efficient route. Smoking the combustion products of the plant material is the most common mode of administration. Vaporization, where the marijuana is heated to its vaporization point causing release of the cannabinoids with water vapor, is another common method. In addition, medical cannabis can be incorporated into food-products intended for ingestion or brewed as a tea. THC is readily absorbed via this route, but results in a delayed time of onset and longer duration of effect as compared to inhalation.¹⁰

Smoking of the plant material results in rapid and efficient delivery of THC to the CNS. Peak concentrations vary greatly between users and are influenced by a variety of factors including the number of puffs taken and hold time. In one study, peak concentrations of THC were reached after an average of 9 minutes.¹⁰

Oral administration of cannabis results in a much slower uptake compared to inhalational methods. Peak concentrations vary considerably, and range from 2-6 hours. There can also be a second peak as the drug undergoes enterohepatic recirculation, wherein a portion of the compound is absorbed by the intestine, transported to the liver, excreted into the bile, and then reabsorbed by the intestine.¹⁰

THC is highly lipophilic and rapidly distributes to the tissues. This can lead to deposition in the lipid stores of chronic users who can exhibit positive THC drug screens for several

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days to weeks after cessation of use as the THC reaches a new equilibrium. The high lipophilicity also results in the transfer of THC into the breastmilk.

Primary metabolism of THC occurs in the liver via the cytochrome P450 system. Specifically, 2C9, 2C19, and 3A4. In the case of oral ingestion, first-pass metabolism limits the amount of THC available to be absorbed. The slowed uptake results in a longer time to peak effect and a longer duration of effect. Carboxylated and hydroxylated metabolites are more water soluble and are excreted in the feces and urine.

Formulations by other routes such as rectal, intravenous, and transdermal, exist, but are uncommon or still in experimental stages.

Clinical Effects

Medical cannabis has been approved in Arizona for several indications, as outlined in a previous module. These are listed below with mechanisms, if known.

- Cancer - The primary use of cannabis in individuals with cancer is for treatment of associated conditions as opposed to the cancer itself such as cachexia, pain, and nausea.
- Glaucoma - Cannabis can decrease intraocular pressure in up to 60% of users via CB1 receptors in the ciliary body.⁹ This effect is independent of the route of administration.
- HIV(+) - Use of cannabis in individuals with HIV is not for primary treatment of HIV, but rather for resultant conditions and treatment side effects such as nausea and wasting syndrome.
- Hepatitis C - Used for pain and appetite stimulation
- Amyotrophic lateral sclerosis - Used as an anti-salivary agent to help prevent aspiration pneumonia as well as for appetite stimulation and pain.
- Crohn's disease - Used to treat secondary symptoms including pain and nausea.
- Agitation of Alzheimer's disease - Used as an appetite stimulant
- Post-traumatic stress disorder - Individuals with PTSD have demonstrated an increased availability of CB1 receptors. Used to treat symptoms of hyperarousal and sleep disturbance.
- Cachexia or wasting syndrome - Used as an appetite stimulant to promote nutrition and weight gain
- Severe and chronic pain - Primarily studied for neuropathic pain

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- Severe nausea - Studied for use in chemotherapy induced nausea and vomiting.
- Seizures - Used for intractable epilepsy
- Severe and persistent muscle spasms - Primarily studied in individuals with spasticity secondary to multiple sclerosis.

Activation of the cannabinoid receptor affects a variety of brain functions:

- Motor activity
- Motor coordination
- Short-term memory
- Reasoning
- Appetite
- Level of alertness
- Pain perception
- Nausea

The most common effect reported by users is relaxation. Other subjective effects include a feeling of heightened senses, a feeling of the slowing of the passage of time, giddiness, laughter, and increased appetite. However, feelings of paranoia, fear, panic, distrust, dysphoria, pain, and transient psychosis can also occur. The potential for such diametrically opposed reactions serve to highlight the complexity of cannabinoids on the brain and the brain itself.

In addition to these subjective effects, a number of physiologic effects also occur. After acute use, there is an increase in heart rate and a decrease in vascular resistance. This may result in orthostatic hypotension and lead to dizziness and syncope. A decrease in intraocular pressure can also occur. There is also an increase in blood flow to the conjunctiva, which leads to the stereotypic red eyes often associated with marijuana users.

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POSTTEST

Please answer the following questions by marking the appropriate response:

1. Another name for medical marijuana is:
 - a. Hashish oil
 - b. Cannabis
 - c. Hashish, or hash
 - d. All of the above
 - e. None of the above

2. The primary compound in marijuana responsible for the psychoactive effects that users may experience is:
 - a. Cannabigerol
 - b. Cannabidiol
 - c. Δ 9-tetrahydrocannabinol
 - d. All of the above
 - e. None of the above

3. The primary compound in marijuana responsible for anti-oxidant and anti-emetic effects is:
 - a. Cannabigerol
 - b. Cannabidiol
 - c. Δ 9-tetrahydrocannabinol
 - d. All of the above
 - e. None of the above

4. Oral administration of marijuana has a delayed time of onset because it is not well absorbed.
 - a. True
 - b. False

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5. What chemical property of THC allows it to easily transfer into breastmilk?
 - a. Water soluble metabolites
 - b. Enterohepatic recirculation
 - c. Lipophilicity
 - d. All of the above
 - e. None of the above

6. All of the following are effects of cannabis exposure except:
 - a. Appetite stimulation
 - b. Decreased intraocular pressure
 - c. Dry mouth
 - d. All of the above
 - e. None of the above

7. As reported by users of medical marijuana, the most common effect is:
 - a. Increased appetite
 - b. Paranoia
 - c. Relaxation
 - d. All of the above
 - e. None of the above

Name _____ Date _____

EVALUATION

	Lowest Worst Least				Highest Best Most
1. To what extent did this module meet your needs?	1	2	3	4	5
2. There was a balance between theoretical and practical information.	1	2	3	4	5
3. The time required was appropriate to the content.	1	2	3	4	5
4. The module increased my knowledge and understanding of the topic.	1	2	3	4	5
5. References or audiovisuals were adequate.	1	2	3	4	5
6. Overall, this program was worthwhile.	1	2	3	4	5

7. Additional comments: _____
