Medical Marijuana – Drug-Drug Interactions

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. Understand basic principles of toxicology
2. Estimate whether drugs are likely to interact based on their pharmacology
3. Understand the current state of knowledge regarding drug-drug interactions involving marijuana

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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Overview

This module will help you understand how marijuana can potentially affect other drugs that a person might have taken. These concepts apply whether the drug in question is a street drug (e.g. cocaine, MDMA/Ecstasy, Gamma hydroxybutyrate), a pharmaceutical (e.g. metoprolol, oxycodone, acetaminophen), or an herbal compound (e.g. St John's wort and Echinacea).

You will explore basic principles of drug metabolism and the concepts of drug-drug interaction in general. You'll then examine how those concepts apply to marijuana specifically.

Toxicology Definitions

The body is challenged to rid itself of hundreds of unique compounds in varying quantities every day. Some of these compounds are generated by the body itself (endogenous compounds) and may be toxic if they accumulate; but many come from the outside the body (exogenous compounds). Toxicologists refer to exogenous compounds as xenobiotics. Marijuana and other street drugs are a common source of medically important xenobiotics, however, many others exist including heavy metals, venoms, chemicals, etc. In toxicology, a poison is a more generic term referring to any compound that can harm the body regardless of the source and includes both endogenous and exogenous compounds. Finally, when a compound comes from another living organism, it is a toxin and when it is a toxin that is injected into another organism, it is a venom.

For purposes of the discussion that follows we will use the term xenobiotic (foreign compounds).

The body relies on a variety of mechanisms to remove xenobiotics. These mechanisms can be broken down into two basic categories of metabolism and elimination. Since elimination is more intuitive we will start there.

Drug Elimination

Elimination is a conceptually simple process of placing a xenobiotic outside the body through one of the elimination sites. These include the urine, the GI tract (usually in bile), sweat, or by exhalation from the lungs. The GI tract, for instance, is a tube that runs through the body but that opens to the environment at both ends. Granted, the GI tract contains a complicated micro-environment and the body has a number of tools

to extract compounds from and to place compounds into that environment but it is essentially outside the body. A xenobiotic in the GI tract that is not taken up by the epithelial cells, that does not kill the epithelium, and that does not alter the micro-environment, is essentially harmless even though it could be extremely toxic if absorbed or injected into the body. A common example of a drug with poor absorption is the antibiotic Vancomycin. When ingested it does not enter the systemic circulation so oral doses are only effective against microbes living in the gut. Conversely, when given IV, it does not enter the gut.

The absorption mechanisms in the GI tract are responsible for bringing medications that are swallowed inside the body. These same mechanisms make elimination via the GI tract more complicated as some drugs that are eliminated in the GI tract by the liver are re-absorbed. This is called entero-hepatic recirculation and can lengthen the time it takes to eliminate a drug. In contrast once a drug enters the bladder, reabsorption does not play a significant role.

The liver eliminates xenobiotics by placing them into the bile which then enters the small intestine in the GI tract and thus placing them outside of the body. As just mentioned, sometimes the xenobiotic is reabsorbed in the GI tract.

While the liver is important for elimination, most pharmaceutical xenobiotics are eliminated by the kidneys (renally). The kidneys eliminate xenobiotics by placing them into the urine. Recall from biology class that the kidney has numerous specialized structures of cells individually called a glomerulus through which blood flows. The wall of the glomerulus has microscopic holes that allow portions of the blood plasma to pass into a series of tubules in the kidneys while blocking the passage of the cells and proteins. This effectively separates a fraction of the liquid portion of the blood. The tubules are lined with cells that secrete and absorb different compounds allowing the body to recover useful compounds while allowing dissolved waste products to accumulate into the filtered liquid. The resulting liquid containing waste is called urine. Many xenobiotics are filtered into the urine both at the glomerulus and by secretion in the tubules. In the kidneys, some of the filtered compounds are reabsorbed including both harmful and beneficial xenobiotics.

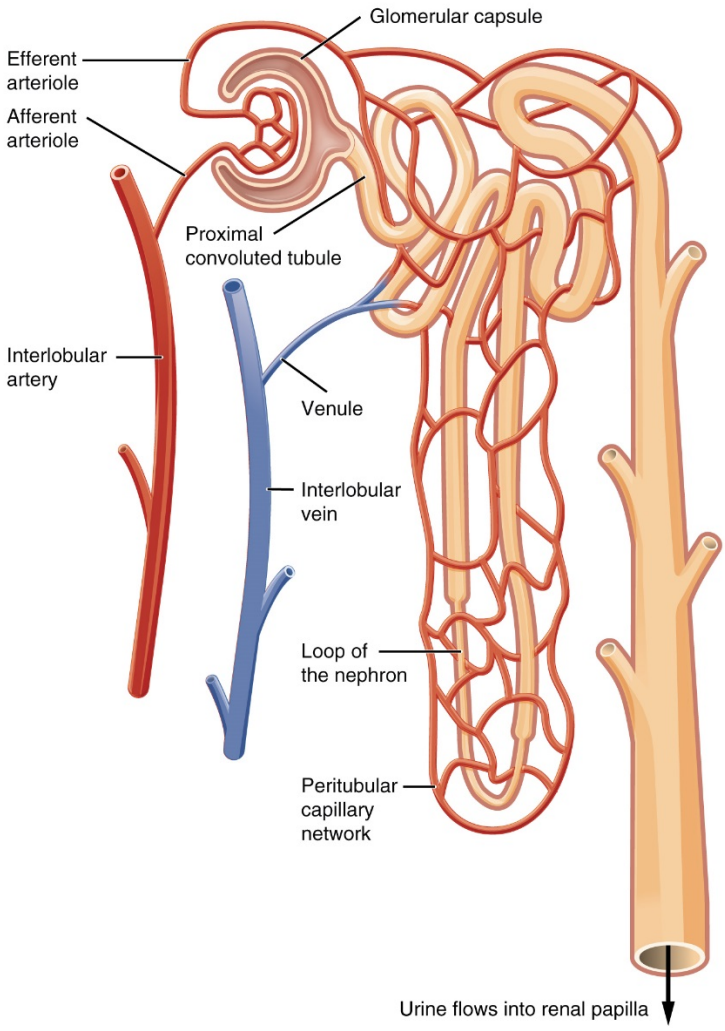

Figure 1 Glomerulus and tubules in the kidney[4]

Xenobiotic elimination is complicated and difficult to predict. While some understanding can be gained by studying the chemical structure of the compound, researchers must ultimately conduct experiments to determine the kidney's and liver's role in eliminating xenobiotics like pharmaceutical drugs. For xenobiotics known to be toxic or for new compounds whose characteristics are unknown, these studies are performed on animals. Animals and humans have many similarities but subtle differences can change the speed of elimination substantially. For pharmaceuticals and other xenobiotics intended for human use, studies are conducted on healthy young adults once the animal studies are complete. As people age, the function of both the liver and kidney decrease and can delay the elimination of xenobiotics substantially. So, the results of elimination studies have to be interpreted with caution in advanced age and with disease. An example of the worst case is that of the dialysis patient with complete renal failure. In this case, elimination by the kidney is completely stopped and xenobiotics reliant on renal elimination can accumulate to dangerous levels even if given following normal dosing.

The other routes of elimination such as sweat and exhalation usually do not play a clinically significant role so we will not discuss them here.

Drug Metabolism

While some drugs have a sizable fraction of the active compound eliminated unchanged, most require some level of modification before they can be eliminated. Metabolism is the chemical reactions that the body uses to change xenobiotics. Most typically, compounds are changed in ways that make them more water soluble so that they can be eliminated renally but sometimes changes are made that increase elimination through the other pathways such as excretion into the bile by the liver. Sometimes compound are metabolized completely into fundamental waste molecules like H_2O and CO_2. Usually however, metabolism results in changes that leave recognizable parts of the molecule.

The body uses a set of chemicals called enzymes to carry out chemical reactions in a controlled manner. Enzymes are not consumed by the chemical reaction that they facilitate; instead, they increase the rate at which a reaction will occur. Each enzyme works on a limited range of molecules called the substrate and they will not facilitate the chemical reactions of other molecules. Thus, the body needs hundreds of enzymes to carry out cellular function. At the most basic level, enzymes join two compounds together or cleave a single compound in two.

The body can regulate enzymatic reactions by changing the quantity of enzymes available or by making different forms of enzymes with slightly different affinity for the reaction. When the quantity of an enzyme increases or when its capability to carry out the reaction increases, it is said to be induced. When the quantity decreases or its ability to carry out the reaction decreases, it is said to be inhibited. Induction and inhibition are key to understanding drug-drug interaction.

Enzymes are in every cell and are responsible for the fundamental chemical reactions that allow for life. There are critical enzymes necessary for all cells to carry out basic cellular functions that do not vary from cell to cell. Other enzymes are expressed in different quantities depending on the cell's role in the body. The most important organ in the body for xenobiotic metabolism is the liver as it expresses a core set of enzymes called the cytochrome P450. Other organs such as the kidneys and lung also metabolize xenobiotics using cytochromes but they usually do so to a lesser degree and do not contain as many types of cytochrome P450 enzymes as the liver. Overtime, scientists realized that many cytochrome P450 enzymes existed and they classified them using an alpha-numeric system that grouped them by characteristics important for researchers but less important for our discussion. Eventually they also realized that

there are mutations (AKA isoforms) of some of the cytochrome enzymes and that these are responsible for subtle variations in their function. Some common medically important cytochrome p450 enzymes are: 2C9, 2C19, 2D6, 2E1, 3A4.

Metabolism is traditionally thought to occur in two distinct phases. Both phases typically increase the water solubility of xenobiotics. Phase I metabolism changes some of the chemical side groups on xenobiotics. Some phase I changes increase the solubility of the xenobiotic while some facilitate Phase II reactions. Phase II metabolism joins larger molecules such as sugars to the xenobiotic. Even though we tend to think of metabolisms as occurring in two distinct stages with Phase I preceding Phase II, the reality is that the enzymes react to substrates and do not follow our rules. This means that if a particular xenobiotic has a Phase II site and a Phase I site, the Phase II change will occur independently of the Phase I change. If however a Phase II site requires a Phase I change then the Phase I change must occur first.

Multiple enzymes may act on the same molecule at different sites so the same xenobiotic may result in many products, some of which may have either therapeutic or toxic effects. These products may in turn be further metabolized. Usually just a few enzymes have high affinity for the compound and therefore act as the primary pathways producing the majority of the metabolites. In large ingestions, the primary pathways may become overwhelmed allowing secondary pathways to play a more prominent role in metabolizing the xenobiotic.

The Role of the Liver

The liver is the primary site of drug metabolism since it contains the highest quantity and most numerous types of cytochrome P450 enzymes. Its role is also facilitated by its position in the circulation because all blood leaving the GI tract passes through the liver. This allows the liver to process the raw materials in food and to detoxify many compounds found in food before they can reach the systemic circulation and be distributed to the body. Anatomically, the liver is arranged into a series of lobules around a central vein that are branches of the portal vein. Oxygen depleted blood laden with carbohydrates, fats, proteins, and toxins from the GI tract is carried by the portal veins to the liver where it enters at the edge of the lobules along with a small amount of oxygenated arterial blood from the general circulation carried by arteries. The blood passes by the hepatocytes (liver cells) which process nutrients and metabolize xenobiotics. The blood then returns to the body via the hepatic vein. The roles of the hepatocytes vary subtly from the edge of the lobule toward its center. The cells containing the highest concentration of cytochrome P450 enzymes are located at the center of the lobule near the central vein. Thus toxic compounds generated by the

action of the cytochrome p450 enzymes will often have characteristic central lobular liver damage.

We mentioned earlier that the liver is the primary location for xenobiotic metabolism but keep in mind that other tissues express varying amounts and a more limited range of types of cytochrome p450 enzymes. In particular this understanding is important for large ingestions as the other tissues may be damaged if a toxic metabolite is produced.

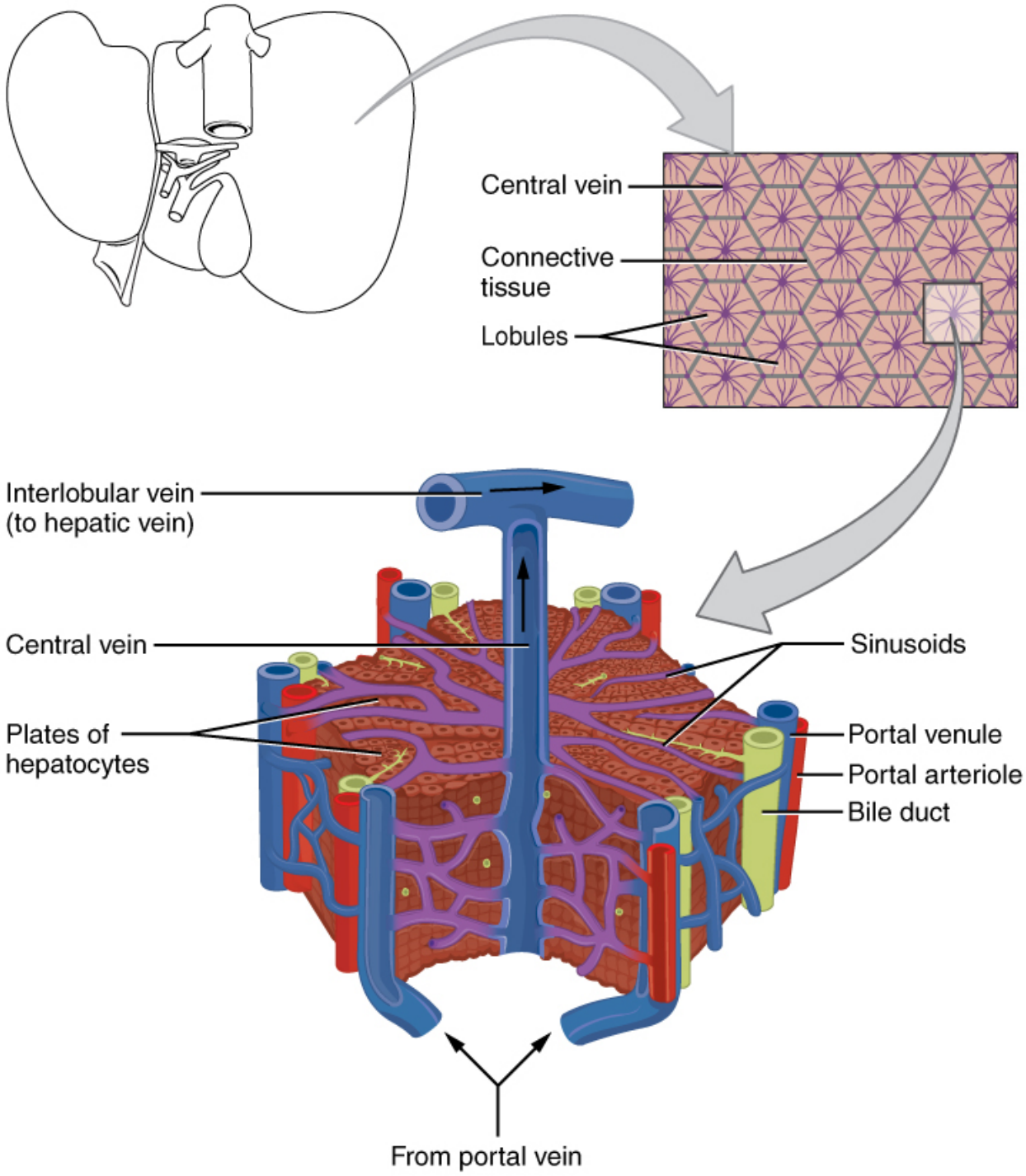

Figure 2 Liver Anatomy[5]

Drug-Drug Interactions

Drug-drug interactions are common. There are several different types of reactions that can occur. Some reflect changes to how compounds are metabolized and some represent changes in how the drug affects the body.

Drug-Drug Interactions

So far we have discussed that xenobiotics including drugs are metabolized by enzymes primarily located in the liver lobules near the central vein and we know that the level of enzymes can sometimes change (but we have not yet discussed why). First we will consider what happens if more than one xenobiotic uses the same enzyme. Later we will discuss how those enzymes levels and activity change. In this section, we will simplify our terminology and limit our discussion of xenobiotics to pharmaceutical drugs.

The simplest form of drug-drug interaction occurs when two drugs are metabolized by the same enzyme but one has a higher affinity for the enzyme. When this occurs, we say the drugs are in competition with the higher affinity compound out-competing the lower affinity compound. Metabolism of the lower affinity drug will be slowed or halted while processing of the higher affinity drug continues at a more normal rate. If they have equal affinity it is likely that metabolism of both will be slowed but the rate of decline depends on the quantity of enzymes available and the concentrations of the drugs. If there is a large amount of enzyme available then processing may continue normally. If a large concentration of drug overwhelms the number of enzymes then processing may be delayed. Overall this concept is similar to the preferred traveler check-in line at an airport counter. As long as someone is in that line, people waiting in the regular line will not be checked in. A medically common example occurs when a patient drinks both ethanol and ethylene glycol. As long the ethanol concentration is above ~100 mg/dL then ethylene glycol cannot be broken down because the enzyme that breaks down both compounds, alcohol dehydrogenase, has a much higher affinity for ethanol. This prolongs the effects of the ethylene glycol but also prevents it from being broken down into toxic compounds.

Sometimes drugs or other xenobiotics cause changes in the quantity of enzymes available or they change speed at which an enzyme works. This results in a net increase or decrease in the enzyme's ability to metabolize drugs. We refer to increased metabolism as induction and decreased metabolism as inhibition. In general, induction increases the number of enzymes while inhibition decreases their function while leaving the quantity unchanged. Induction is slower than inhibition because induction requires the cells to make more enzymes. A common medically important interaction occurs when grapefruit juice inhibits cytochrome P450 3A4 preventing the breakdown of drugs metabolized by the enzyme. This results in an increase in the drug levels which can have serious effects. For instance, grapefruit juice inhibits the cytochrome P450 3A4 enzyme that breaks down coumadin (Warfarin). This can result in a dangerous

accumulation of coumadin in the body leading to inability to form blood clots (coagulopathy) such that even ordinary activity can cause significant bleeding.

Direct Drug Effect Changes

Now that you understand the basics of how enzymes affect drug metabolism, let's consider how drugs can interfere with each other at the point of function. Drugs are taken to change the way cells function by altering a biochemical pathway and creating a clinically important effect. To do this, they influence the molecules in the cell. Often this takes the form of binding to cellular proteins to alter their function. Other mechanisms also exist but we will limit our discussion to protein binding. The bound protein may be the end product of the therapeutic pathway but it may also just be the start of a cascade of proteins that culminates in the desired effect.

Proteins themselves are often large molecules with many sites at which a drug can bind. This means that a single protein can be affected by multiple drugs. Conversely, a single drug can affect multiple proteins because, even though the body makes thousands of different kinds of proteins, proteins often have similar regions on them. This means a single drug could potentially bind many proteins other than the desired target as long as they share similar binding sites. As we mentioned earlier, proteins are often part of a complicated interacting web. Different drugs can bind different proteins in the pathway.

Drugs that affect the same protein or pathway can increase or decrease each other's function. The degree to which one drug affects another can be straight forward addition of their effects. Additive effects can be thought of as 1+1=2. Sometime drugs can interact in ways that cause them to have unexpectedly large effects when combined. This is called synergy and can be thought of as 1+1=5. Synergism is also often referred to as potentiation. Finally, if two drugs interact in a way that decreases their overall effect, then they are said to be antagonists.

Complicating Factors

Several factors complicate our understanding of drug function. The first is that individual people often have variations in the genes that encode the proteins and thus changes in the proteins themselves. These variations arise from a variety of mechanisms that result in changes to the person's DNA and are commonly referred to as mutations. Mutations that affect drug metabolism affect all the cells in the body and are inherited from parents or from unique mutations in either the sperm or egg that combine at inception. In this latter case the mutation would not present in either parent. Sometimes genetic changes do not alter the protein coded by the gene because there is some redundancy in the genetic code. Sometimes minor changes result that increase or decrease the proteins function slightly and usually have no

significant effect. Other times, the protein is completely non-functional or hyper-functional. When mutations occur, proteins are often thought of as having a percent function based on a reference version of the protein. The blood clotting factors, for instance, are typically reported in this way. So you may hear that a hemophiliac has 25% factor VII function. On a day-to-day basis these variations may have little effect but may become important when exposed to certain environmental conditions, when exposed to xenobiotics, or over the long term due to subtle changes in cellular function. Sometimes these changes can have profound effects resulting in severe disease or death. A practical example can be seen from individuals with variations in their response to codeine. Many of us have met patients for whom codeine does not work. This happens because codeine must be converted to morphine before it will have a clinical effect. Some people contain a version of the gene that does this slowly. Sometimes the codeine to morphine conversion is so slow that no clinically significant morphine level will accumulate. Conversely, there are case reports of profound respiratory depression occurring at normal codeine dosing in people who have very efficient versions of the protein. In this case, conversion of codeine to morphine occurs very quickly and levels of morphine can be high enough to cause respiratory depression. On a day-to-day level, the differences in the proteins that break down codeine do not seem to matter, but clearly are important with codeine exposure.

The second factor is that there are two copies of each gene, each with potentially different mutations. The effects of a drug can therefore be a mixture of the effects of both gene versions present in an individual. Sometimes, we anticipate that certain mutations are present in an individual based on their ethnicity as some mutations are common in different areas of the world and doctors can use this to guide drug therapy. In the United States, the "melting pot" combines many different ethnicities making for sometimes unexpected genetic diversity based on outward appearance so providers must be alert for potential genetic effects.

The third complicating factor is that drugs may affect multiple proteins either in the same cell types or across different tissues and these effects may be dose dependent. Therefore sensitivity to the drug depends on not only the individual genes expressed in the target tissue but also on genes expressed in other tissues in the body.

The fourth factor that complicates our understanding of drug function is that we do not fully understand cellular biology. Researchers continue to refine our understanding but our knowledge is incomplete. Thus the impact of a compound is often imprecisely understood. We rely on a biologic models, in vitro studies, animal studies, and then human studies to gauge both the beneficial and negative impact of drugs. Most of the time our understanding is good enough but sometimes unexpected problems arise that results in drugs being withdrawn. Thalidomide is the classic example of such an

interaction. It is an excellent drug to treat nausea but it can cause critical harm to fetal development. Unfortunately, the fetal harm was found only after release to the marketplace.

Even though our understanding is incomplete, most people fall within a predictable spectrum of drug effects. From a therapeutic standpoint using prescription drugs, doctors adjust the medication based on its clinical effects while monitoring for side effects. That is why some people take more medication than others even at the same body weight. Of course, this supposes that the patient is taking the medication as directed.

Marijuana Specific Information

This section outlines what we know about drug-drug interactions with Marijuana. As you'll see, we know enough to make educated guesses but there is little specific information.

What Compounds are in Marijuana

Products from the marijuana plant, *Cannabis sativa*, are smoked or eaten for their psychoactive compounds. The most widely recognized compound is delta-9-tetrahydrocannabinol (delta-9-THC) but many other similar compounds can be found in marijuana. Collectively these compounds are referred to as cannabinoids. To date, at least 70 different cannabinoids have been discovered.[1] In addition to these compounds, more than 400 other compounds are present.[1] Finally, smoking or other methods of extracting the psychoactive components can create compounds that result from the extraction processes like burning or alcohol extraction. In the case of smoked marijuana, these compounds are similar to those found in tobacco smoke.[2]

Understanding what compounds are in marijuana is complicated by the fact that marijuana is a natural product grown in a variety of different conditions and there are many cultivars. Also, the psychoactive compounds vary throughout the plant with relatively little in the roots and stems while the flower buds contain significant amounts. Finally, a variety of products are available from plants to oils extracted with a variety of processes.

Marijuana Metabolism, Elimination, and Drug-Drug Interaction

Marijuana's principle compound delta-9-THC undergoes metabolism primarily via liver cytochrome P450 enzymes 2C9 and 3A4. A wide variety of both active and inactive compounds are created during metabolism. It is eliminated by the GI tract in the feces and by the kidneys in the urine with roughly 50% and 15% elimination respectively at 72 hours. The drug remains detectable for several days following a single use.

Cytochrome P450 2C9 and 3A4 enzymes are the principle sites of metabolism for many different drugs besides cannabinoids. Of the two, 3A4 metabolizes more compounds than does 2C9 but both are responsible for many clinically important drugs. There are numerous other cytochrome enzymes which may be affected by marijuana use but the data to date is limited and the clinical effect of these enzymatic changes is uncertain.[3]

The best data for drug-drug interaction with marijuana comes from the two commercial preparations derived from marijuana, Nabilone and Dronabinol. Their package inserts list a variety of possible interactions as shown in the table below.

As can be seen from the table, the majority of interactions appear to be additive in terms of sedation and cardiovascular effects. It is therefore reasonable to assume that marijuana will alter drug metabolism so first responders and providers should consider changes in marijuana use both in terms of route, quantity, and brand when evaluating for medication interactions.

Table 1 Potential drug-drug interactions for Nabilone[6]

Drug/Drug Class	Clinical Effect
Amphetamines, cocaine, other sympathomimetic agents	Additive hypertension, tachycardia, possibly cardiotoxicity
Atropine, scopolamine, antihistamines, other anticholinergic agents	Additive or super-additive tachycardia, drowsiness
Amitriptyline, amoxapine, desipramine, other tricyclic antidepressants	Additive tachycardia, hypertension, drowsiness
Barbiturates, benzodiazepines, ethanol, lithium, opioids, buspirone, antihistamines, muscle relaxants, other CNS depressants	Additive drowsiness and CNS depression
Disulfiram	A reversible hypomanic reaction was reported in a 28 y/o man who smoked marijuana; confirmed by dechallenge and rechallenge
Fluoxetine	A 21 y/o female with depression and bulimia receiving 20 mg/day fluoxetine X 4 wks became hypomanic after smoking marijuana; symptoms resolved after 4 days
Antipyrine, barbiturates	Decreased clearance of these agents, presumably via competitive inhibition of metabolism
Theophylline	Increased theophylline metabolism reported with smoking of marijuana; effect similar to that following smoking tobacco
Opioids	Cross-tolerance and mutual potentiation
Naltrexone	Oral THC effects were enhanced by opioid receptor blockade.
Alcohol	Increase in the positive subjective mood effects of smoked marijuana

Questions

1. Which of the following diseases would most likely result in changes to drug metabolism
   A. Cardiac disease
   B. Kidney disease
   C. Liver disease
   D. Lung Disease

2. Dug metabolism refers to which of the following
   A. How drugs get into the body when taken orally
   B. The effect the drug has on the body
   C. The chemical processes that change drugs in the body
   D. The role the kidney plays in removing drugs from the body

3. Drug metabolites may be toxic
   A. True
   B. False

4. Drug metabolites may have harmful and beneficial (therapeutic) effects
   A. True
   B. False

5. Marijuana has well described drug-drug interactions
   A. True
   B. False

Name: _____
Date: _____

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EVALUATION

	Lowest Worst Least				Highest Best Most
1. To what extend 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:_____

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