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Synthetic Cannabinoids: Law vs. Science

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Synthetic Cannabinoids: Law vs. Science

Honors Thesis
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Synthetic cannabinoids are designer drugs which have been made to mimic the effects experienced by tetra-hydro-cannabinol (THC). These substances are sprayed on herbal blends and ingested through smoking. There are many different structures of synthetic cannabinoids because the Controlled Substance Act has outlawed certain structures. A chemist can alter an already known structure by changing a minor detail creating a new legal drug. The problem with these drugs is that they cause many adverse effects and are bad for public health. In order to decrease the use of these synthetic substances the legalization of marijuana is being considered. The issue with legalizing this now controlled substance is that the effects on driving. There is no way to directly correlate the level of THC in the blood to the effects an individual is experiencing. Colorado has legalized recreational marijuana and has not experienced many issues thus far. A new technique for DUI testing needs to be found in order to be sure marijuana legalization is efficiently regulated and the public is safe.

Keywords and phrases: Thesis, honors thesis, undergraduate research, marijuana, synthetic drugs, cannabinoids, THC.
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Synthetic drugs of all varieties have become a severe problem in the United States in recent years. Experimentation and minor altering of known illicit drugs in all forms allows these substances to be legally obtained, leading to misuse and adverse effects. The law has taken action against these drugs and knows the severity of their effects on health and public safety. Synthetic cannabinoids have been the most recent substances on the market and are continuing to be used despite how unsafe they are. More action needs to be taken and a possible solution is legalizing the natural form of these substances, marijuana. A few states have now legalized natural marijuana and it should not be too long before other states see that it is not a bad option. The only problem is that there needs to be more testing done on how this substance is affecting individuals, specifically while driving.
What is a synthetic drug?

A synthetic drug, also known by the term designer drug, is a psychoactive substance that has been created due to research and experimentation with previously existing substances. They are usually modeled after known illicit drugs whether it is their stereoisomer, salt form, or a derivative. There are usually very minor details that are changed structurally creating a new substance. Grant Smith of the Drug Policy Alliance stated that "It's easy for entrepreneurs in US labs or overseas to manipulate the molecular structure and come back with another product promising the same kinds of highs" (Wood, 2012). This process of alterations can continue from the original drug to the first alteration, second alteration, and so on. This process usually produces very potent substances that vary in effects and the severity of these effects. Even though these drugs have different chemical structures, they can still have the same effects. Some structures that are more similar to one another could have completely different effects; it just depends on substitute groups and how the alteration affects the overall outcome of the product.

There are many different types of synthetic drugs in different drug classes including opioids, psychedelics, stimulants, sedatives, steroids, and cannabinoids. Some of the most well-known synthetic drugs right now are bath salts and spice. There have been many stories about these drugs in order to let the public know how dangerous they are. The Office of Natural Drug Control Policy Director Gil Kerlikowske even mentioned that “synthetic drugs cause substantial damage to public health and safety” (Leger, 2012). Bath salts are a
stimulant and spice is a mixture of cannabinoids. Cannabinoids have been the most prevalent problem for the government thus far.

**What is a cannabinoid?**

A cannabinoid is a substance which has a three ringed structure with an alcohol which does not contain nitrogen. There is a benzopyran and there can be an acyclic ring within the structure as well. Below are some examples of cannabinoid structures:

Cannabinoids are the active compounds in cannabis substances which are most commonly ingested through smoking. Marijuana itself contains 61 cannabinoids which, if smoked, metabolizes into many other forms of those substances. THC itself metabolizes into 11-hydroxy-THC, 11-nor-carboxy-THC, and glucuronide metabolite. The delta 9 THC form is the psychoactive ingredient in natural marijuana. Synthetic marijuana laced on plant material was first
reported in the U.S. in December 2008 and from then the variety began to expand exponentially (Office of National Drug Control Policy, 2012). These new forms go by many names with the most popular being synthetic marijuana, fake weed, K2, and spice (Culver, n.d.). The synthetic forms of marijuana are mimicking the effects and structure of THC as seen below:

The delta 9 form of THC is on the left and a synthetic cannabinoid HU-210 is on the right. There were only two small modifications made to THC in order to produce this new substance. The first modification was to the top of the molecule where there is an alcohol replacing the methyl substituent. The second modification was to the carbon side chain. It was made longer and there are now methyl substituents off that chain. Once there were many modifications to the structure of THC people started playing around with other types of structures which produced similar effects. There are many different types of structures that now exist.
JWH-018

These structures were only modified by changing the length of the carbon side chain. This is a very simple modification for scientists to perform, creating many possible structures for new synthetic compounds.

AM-2201

These structures were altered by changing the functional group of the side chain. This modification is a little more difficult than the previous, but still simple enough for the developers to create many variations.

JWH-072

JWH-200
These modifications were made on a different part of the structure other than the side chain. They can get more complicated and require more steps than the side chain alteration. This also has a greater impact on the difference between the potencies of the compounds.

These last two structures show the complex modifications that are being created in order to stay ahead of legislation. These are completely different structures, making it more difficult for the law to predict the next generation of
structures that will be developed. Although these drugs all produce the desired effects, their structures vary greatly. Even with the many different structures possible for synthetic cannabinoids they all work the same way in the body.

**Pharmacokinetics and Pharmacodynamics**

Pharmacokinetics is the study of how drugs move throughout the body or what the body does to the drug whereas pharmacodynamics is what a drug does to the body. Once ingested, drugs generally go into your blood stream. In your blood, there are many different receptors that these drugs can attach to in order to create a biological response. The two receptors for cannabinoids, such as synthetic marijuana, are the CB1 and CB2 receptors. The CB1 receptor affects the central nervous system and the CB2 receptor affects the immune system. The psychoactive effects experienced after the use of cannabinoids is due to the CB1 receptor. The CB1 receptor is also responsible for the effects on memory, emotions, cognition, and movement. Cannabinoids are agonists for the CB receptors meaning they initiate a physiological response when creating a complex (Gurney, et al., 2014). Natural marijuana is a partial agonist for these receptors whereas synthetic forms, such as spice, are full agonists (Messick, n.d.). This means that the synthetic substances are more potent, creating stronger effects whether desired or adverse.

There are many different effects due to cannabinoid ingestion which are similar for natural and synthetic marijuana. A lot of the effects depend on the setting where the usage takes place and it can be different depending on who
you are with. There are different types of effects that cannabinoids have on the body including behavioral, physical, and reproductive. The behavioral effects include Euphoria, relaxation, altered time perception, lack of concentration, impaired learning, memory and mood changes, enhanced visual and olfactory senses, and disorientation. Some physical reactions include increased heart rate, heart attack, dry mouth, increased appetite, decreased respiratory rate, immune changes, lung damage, and psychomotor impairment. There are not many reproductive effects but they include reduced testosterone levels, reduced sperm count, and increased abnormal sperm for men. For women the main effect is the reduction of the lutenizing hormone which helps the fertilized egg be planted in the uterus. This drug is very addictive and can cause many withdrawal symptoms as well. Symptoms of withdrawal are restlessness, irritability, mild agitation, hyperactivity, insomnia, nausea, cramping, decreased appetite, sweating, and increased dreaming.

After the physiological response occurs, the drug must be excreted somehow. Cannabinoids are lipid soluble and protein bound. This means that they will be stored in the fat cells of the body and not immediately excreted. Only about 35% of what is ingested is excreted in the urine and the rest is stored in the body. These substances typically have a 3-4 day half-life. This changes when looking at a chronic user. Since they are ingesting more constantly there will be more of the drug stored in the body and it will stay for a longer amount of time before getting excreted.
Are these drugs legal?

Some synthetic drugs are legal and some are not. There are two different acts that contribute to the legal status of marijuana and synthetic marijuana. These acts are the Controlled Substance Act and the Synthetic Drug Abuse Prevention Act of 2012. The Controlled Substance Act is the United States’ federal drug policy. Substances are made illegal under this act according to structure only, not by effects. This can cause problems because it takes so long for the government to get enough reliable research to make a substance illegal that, by the time the end that process and it gets added to the list of controlled substances, there are already multiple new structure variations on the streets. Substances are scheduled from I to V with schedule I being the highest risk and V being the lowest risk. Drugs are placed in these schedules based on known factors such as potential for abuse, scientific evidence of pharmacological effects, state of current scientific knowledge, history and current pattern for abuse, scope and duration of use, significance of abuse, risk to public health, physiological dependence liability, and whether it is an immediate precursor of an already controlled substance. An immediate precursor is defined as the principal compound used in the manufacture of controlled substance, a chemical intermediary likely to be used in manufacture of controlled substances, or where control of the substance is necessary to limit manufacture of controlled substances. This is decided by the attorney general. If a substance is to become scheduled, the Drug Enforcement Administration and the Food and Drug Administration (FDA) together will decide on which schedule it will be placed in.
The Synthetic Drug Abuse Prevention Act was created once the government started seeing such an increase in synthetic drug use. Since it was becoming such a problem, they created this act so that synthetic drugs, such as synthetic cannabinoids, could be placed in to schedule I under the Controlled Substance Act. Natural marijuana is a schedule I drug under the Controlled Substance Act meaning it has high potential for abuse, has no currently accepted medical use in treatment in the US, or that there is a lack of accepted safety for use of the drug under medical supervision. With the Synthetic Drug Abuse Prevention Act in place, some synthetic cannabinoids have been temporarily placed under schedule I. Anything that is found to be a cannabinoid CB1 receptor agonist is classified under schedule I. Most of the more popular known synthetic cannabinoid structures have been banned for this reason but the small modifications that are being made to structures are allowing the new substances to be legal. The Controlled Substance Act was amended in 2012 the same year that synthetic cannabinoids became schedule I. This amendment increased the amount of time that a substance could be temporary scheduled. Prior to 2012 a substance could be temporarily scheduled for a year with an extension of six months compared to now, where it will be scheduled for 2 years with an extension of up to a year. They extended this time period due to the overwhelming amount of new products that were being made and to allow them more time to find evidence on certain structures to get them permanently scheduled. Now that all these substances are getting temporarily scheduled people are finding ways to get around the law.
How are people getting around the law?

Some people get around the law because they are selling incense. Incense is a substance that is meant to be burned producing a certain fragrance. This substance contains synthetic cannabinoids but is labeled “not for human consumption.” Since it contains that label, it is technically legal to sell. The problem with this is that people buy incense with the intent of smoking it; therefore, they are basically purchasing synthetic marijuana right in convenience stores and other places it is being sold. It has been recognized by the public that this is an issue and Rosenbaum, Carreiro, and Babu agreed by saying that we need to “develop rapid and agile strategies to recognize and report new ‘legal highs’ as we encounter them” (2012). The other way that people get around the law is just slightly modifying the structure of the current drug like I mentioned earlier. Due to these small changes in structure, there is too much variation between all the different synthetic cannabinoids. By the time the law gets enough testing done on one drug there are already multiple other forms of that drug being distributed to the public.

Why are people using these synthetic forms?

People are still using these synthetic drugs because they want to avoid getting into trouble with the law. Synthetic cannabinoids do not show up on the typical workplace drug screen so, if people use these substances instead of the natural form they will not risk positive drug tests. This is especially popular for previous users who may be on probation (Stephens, p. 15); they would rather
risk the adverse effects by using the legal form of a drug than risk getting caught with an illicit drug. Another reason is the easy access. There are no, for lack of a better term, middle men. Someone can walk right into a convenient store and pick up whichever product they are looking for and they can get it at a lower price than the natural form. People are looking for the easiest and cheapest way to access the high they desire. What people do not realize is that they may not experience the same exact effects and the same level of an effect as with natural marijuana.

Since there are so many people using these substances, there needs to be an alternative to decrease the amount of people abusing those drugs. A method that has been projected is the legalization of natural marijuana, which a few states have taken head on. The DEA was against legalization because they thought that it would increase abuse and addiction (Drug Enforcement Administration, 2010). The counterargument for that is that if people want to smoke, they will find a way which is why people are abusing more harmful substances (the synthetic forms). Legalization may increase use but, that does not mean it will increase addiction or abuse of the drug. Colorado and Washington have legalized marijuana for recreational use and there have been many benefits to this. Colorado has had a plan since the beginning of the talk of legalizing marijuana and is proving to the rest of the United States that is was not a poor decision.
How is Colorado doing it?

Marijuana has been legal in Colorado since December 10th, 2010 for medical use and since November 6th, 2012 for recreational use. Recreational marijuana was legalized because of amendment 64. This allows for personal use and growth within limits. According to this amendment, anyone 21 years of age or older may legally possess up to one ounce of marijuana. This can be bought at any store that has been licensed to sell natural marijuana (Ingold, 2013). These shops work like the liquor stores now. You can go in and pick out what you want and how much you want and then you have to show your ID to prove your age before purchasing. You may buy up to an ounce at a time if you are a Colorado resident.

There is no rule saying that you cannot purchase from more than one store in a certain period of time which allows people to purchase more than the legal amount. Someone could go into one store and buy an ounce, and then go into another store and buy another ounce. If they get caught with over the legal limit then they will get into trouble with the law. Most people do not buy an ounce at a time because that is a lot. An ounce of marijuana can be thought of like a keg of beer. One person cannot consume that amount unless they are in it for the long haul. Most people will typically buy an eighth. People who want to buy with an out of state license can only buy up to a quarter ounce (Ingold, 2013).

Prices for natural marijuana can vary from store to store, but it usually costs around $150 - $300 for an ounce. An eighth, the most popular buy, is about
$20 - $45. The tax on this product is around twenty percent. This means that on a $30 purchase the tax is about $6. This is relatively high, but people are willing to pay it to get the product they want. In Denver, there is an extra $2.59 tax which raises the tax to about twenty-eight percent. Many people who are against legalization make the argument that if it is legalized the price will go down, therefore increasing the number of marijuana users (Office of National Drug Control Policy, 2010). It can be seen that, at least in Colorado, it is not cheap and the taxes are extremely high, making that argument invalid. This begs the question, where is all this money going?

The first forty million that is made off marijuana sales is going towards school construction whether it be remodeling, fixing problems, or building new schools entirely. The rest of the money is going towards regulation of the licensed stores. Right now there are cameras in all the stores but there is not much security past that. There is no customer list or anything that shows who is buying what and how much. A database like that would be something to look into for the future for regulation purposes, but right now amendment 64 forbids the government from knowing details about natural marijuana purchases. The money is also going to go towards educational campaigns. These campaigns would teach people how to safely use these substances and make sure everyone understands the laws behind the amendment. They believe that education is very important when dealing with the law.

Once people buy their products, there are also rules on where marijuana can be consumed. Public consumption is banned but there are designated
smoking areas. These work like smoking areas in large smoke free parks. There are certain areas that are marked that people are allowed to smoke in. The only difference is that these smoking areas are for marijuana and not cigarettes. There are also restrictions in some neighborhoods. Some neighborhoods say that you cannot smoke on your front porch or driveway or back porch. Basically, you must be inside your house so that the smoke will not bother those around you. In some places you are allowed to smoke anywhere on your private property, it just depends on where you are at in the state.

What is the problem?

The main problem that people, government, and consumers alike, are worried about is the effect of marijuana on driving. Marijuana has been found to be in drivers’ systems when crashes have occurred, but any deaths cannot be directly related to it. Right now, the legal driving limit in Colorado is 5 ng/mL of blood. This works like the legal driving limit for alcohol. They look for signs that someone is under the influence and then pull them over. If someone’s blood test comes back with a level of 5 ng/mL or higher they are determined to be “under the influence” and get arrested for DUI. Right now the penalties for a first offense DUI is county jail time for a minimum of five days in the county jail with a maximum of one year, a fine of $600-$100, 48-96 hours of community service, and possible probation for up to two years. The penalties for a second offense include ten days to one year in the county jail, $600-$1000 fine, 48-120 hours of community service, and at least two years of probation. For a third or any consecutive offense thereafter the penalties include sixty days to one year in the
county jail, one year of alcohol and drug safety education classes, $600-$1500 fine, 48-120 hours of community service, and probation for at least two years (Norml, 2014).

There has been evidence that people driving under the influence of THC are compensating for the impairments they endure from the exposure. It has been said that “they tend to drive slower and take fewer risks” (Anderson & Rees, 2013). One sign that someone is under the influence of marijuana while driving include being overly cautious or driving ten or more miles per hour under the speed limit. Even though drivers could be acting more cautious when driving, their actions could affect other drivers who are traveling at a normal speed causing problems.

An issue with this blood test is that the psychoactive cannabinoid tetrahydrocannabinol (THC) does not come out of the body in the same way as alcohol. As I mentioned earlier THC gets stored in the fat cells of the body which means that not all of the substance is being metabolized and excreted at a constant rate. This is especially true for chronic users. This becomes an issue when testing blood for drivers under the influence. Someone could be driving and not be under the influence currently, but test positive if they are a chronic smoker. This is because they may not have excreted all the THC out of their body yet and it is just not coming out of the fat storage. This problem could cause innocent people to be charged with DUIDs. Another issue is that the level of THC in the body cannot be directly correlated to the effects that a person is
experiencing. This issue has been recognized by reliable sources and they are trying to work out a new method for drug testing drivers.

The National Association Traffic Safety Administration has been reviewing the laws and stating their opinion on these issues. They stated that “it is difficult to establish a relationship between a person’s THC blood or plasma concentration and performance impairing effects.” This is very true because, unlike alcohol, THC does not have a normal level scale for certain effects. There are normal effects experienced but, it can be at different levels for everyone and they are not directly related to levels in the blood. Because of this, they also said that “it is inadvisable to try to predict effects based on blood THC concentration alone.” The concentrations of analytes of marijuana are often under 5 ng/mL after three hours but are at different levels than the THC concentration. Because of this, it was predicted that marijuana would have an impact on driving for up to three hours after ingestion. This was proven in open and closed driving courses the National Highway Traffic Safety Administration set up, but further testing does need to be done (National Highway Traffic Safety Administration, n.d.). This means that someone could still be under the influence and their behavior, specifically driving, could be being affected, even though the THC form is not in their body. This is a big issue for blood testing. Another problem is “the lack of reference materials for use in positive identifications present obstacles to analysis” (Agilent Technologies, 2011).

A new form of DUI test is being proposed which is like a Breathalyzer for alcohol testing. This would be a breath test which measures the amount of THC
in the breath. It would work like the blood test but the breath is the matrix rather than the blood. The only issue with this is that you would have to catch someone within a smaller time gap after they smoked than for the blood test. This is because THC does not stay in the breath for too long after exposure. They are working on ways to improve this system and help make the laws fairer to people, as well as making their tests more accurate. Norchem, is a company in Arizona, that has been able to extract synthetic drugs from urine and test them using liquid chromatography, specifically LCMSMS, and detect them. This could be the start of a new way to identify these designer drugs (Norchem, 2011). They are also working on simple methods for identification of synthetic cannabinoids using gas chromatography mass spectrometry (GC-MS) (Gluodenis, 2011). If simple methods for identification are found then it may lead to a new method for DUI testing.

Overall, there needs to be a compromise between the law and the science behind these synthetic drugs. Synthetic cannabinoids are a huge risk to public health which needs to be reduced. If legalization of marijuana can help with reducing the risk of more synthetic substance abuse, then it may be the right way to go. This is only if there is enough development in the area of detection for the effects on driving. If the law and science can work together, then there may be opportunities for all to be satisfied with the results.
Bibliography:


