Acute and Long-Term Adverse Health Effects Related to Use of Medical Marijuana, Hemp with THC, and Kratom

Report Prepared in response to SR 96 of the 2023 Regular Legislative Session

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Contents

Executive Summary

This report is submitted pursuant to Senate Resolution 96 (SR 96) of the 2023 Regular Legislative Session. SR 96 directed the Louisiana Department of Health (LDH or the Department) study acute and long-term adverse health events related to medical marijuana, hemp containing THC, and kratom**.**

Limitations

The resolution directed the Department to study acute and long-term adverse health events related to medical marijuana. LDH does not conduct primary research on the health effects related to medical marijuana nor does it track adverse events related to any of these regulated products. This report was developed by analyzing primary and secondary literature on short- and long-term health-related effects of consuming these products. A notable limitation of the literature is that studies involving cannabis use often do not distinguish between consumable hemp, medical marijuana, legal marijuana, nor illegal marijuana. Adverse health effects shown in the literature will largely mirror those seen with cannabis use with the same extenuating factors such as dosage, frequency, polysubstance use, and pre-existing conditions. The effects of other phytocanabinoids and THC isomers are not considered in this report.

Key Takeaways

- Medical Marijuana / Hemp with THC
    - Research into the beneficial and adverse effects associated with cannabis use is ongoing, and results vary significantly from individual to individual, with both sets of effects requiring additional research as new cannabinoids are discovered and more is learned about the variety of effects cannabis users can experience.
    - Many acute effects of marijuana use are dose-dependent, but a number of issues have been well-documented in the literature as well as anecdotally and include loss of short-term memory, lack of coordination, reduced cognitive ability, tachycardia, reduction in impulse control, and hypertension. On higher doses, users may experience more "negative" effects such as anxiety, paranoia, hallucinations, and confusion.
    - Long-term health effects are not as well documented, but some studies note addiction, amotivational syndrome, cognitive defects, and effects associated with inhalation of substances as potential long-term effects of consuming cannabis.

- Kratom
    - Much is still unknown about kratom and related chemical compounds, the short- and long-term health and safety effects of kratom use.
    - Some studies note Kratom as a substance to combat opioid addiction while others note that it has a high potential to cause addiction. The National Institute on Drug Abuse (NIDA) is conducting studies to better understand potential therapeutic use and adverse effects.

Medical Marijuana

Introduction

The use of marijuana to treat ailments dates to one of the earliest recorded pharmacopeias from ancient China around 2700 BCE (Clark et al., 2011). More recently, it was part of the U.S. Pharmacopeia

(one of two registries of licensed drugs in America—the other is the National Formulary) from 1851 to 1942 (Clark et al., 2011; Martin, 2020). However, the U.S. began to crack down on what was a rather laissez-faire approach to the drug market in the early 20th century; prior to advent of the Pure Food and Drug Act of 1906. For instance, literal snake oil was marketed along with a variety of similar nostrums for virtually any ailment one could conceive—many of which were little more than ethanol enhanced with a few flavorings. That atmosphere changed for marijuana users in 1937 (Rosenthal and Kleber, 1999; Bostwick, 2012; Martin, 2020), when the Marijuana Tax Act created a per-ounce tax of $1 on marijuana used for medicinal purposes and $100 on marijuana for "unapproved uses." Marijuana continued to be legal in the U.S. until the passage of the Controlled Substances Act in 1970, which scheduled marijuana along with substances like heroin, lysergic acid diethylamide (LSD) and psilocybin as a Schedule I drug (Rosenthal and Kleber, 1999; DuPont, 1999; Clark et al., 2011). Schedule I drugs are defined as those having no accepted medical use, high potential for abuse, and an unquantified safety profile. Marijuana is currently listed in Louisiana's own schedule of controlled dangerous substances (La. R.S. 40: 964 et seq.) as a Schedule I hallucinogenic substance (as "Marihuana").

Despite these concerns, a steady trend of legalization of the use of marijuana or cannabis that began in the 1990s continues to this day. Figure 1 shows the status of cannabis in the states and territories of the U.S.; only four (American Samoa, Idaho, Nebraska, and Kansas) currently have no legalized recreational, therapeutic marijuana, or hemp products program.

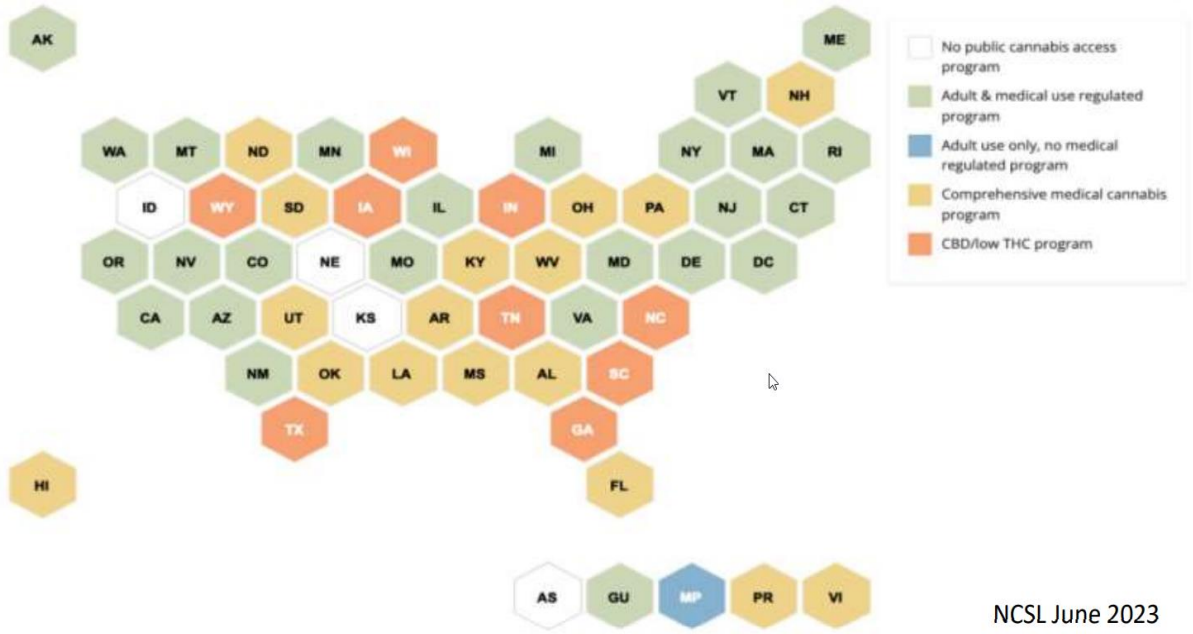

Figure 1: Status of Cannabis Regulation Source: NCSL June 2023

History of Medical Marijuana

In 1996, California passed the Compassionate Use Act (also known as Proposition 215) in the first legal challenge to the federal ban against marijuana use (Martin, 2020). Since 1996, the legal landscape has become a labyrinth of contradictory directives, restrictions, and prohibitions, and until and unless something changes at the federal level, the status of marijuana will continue to be a legal gray area. In

1978, NIDA initiated a compassionate-use program for 20 patients that allowed marijuana grown at the University of Mississippi to be sent to a facility in North Carolina to be packaged into cigarettes sent to the patients' doctors and/or pharmacists (Clark et al., 2011). The cigarettes were used by HIV sufferers to improve appetite and reduce cachexia (wasting syndrome) associated with the disease process. The program was terminated in 1991 due to an increasing number of applicants (Rosenthal & Kleber, 1999).

In 1985, the first two of four currently available (two of which have not yet received FDA approval) cannabis-derived pharmaceuticals were approved in the U.S. as Schedule II/III drugs (Bostwick, 2012). Marinol and Cesamet are synthetic tetrahydrocannabinols (THC), used for the treatment of nausea and vomiting associated with cancer chemotherapy as well as cachexia and appetite loss related to AIDS. These medications have disadvantages relative to traditional forms of (inhaled) cannabis for the following reasons: 1) prohibitive cost relative to the cost of conventional cannabis; 2) difficulty titrating dosages with orally-ingested forms; and 3) occasional poor tolerance of orally-ingested drugs as antiemetics (Clark et al., 2011).

Medical benefits of marijuana are generally attributed to Δ-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) content (Bostwick, 2012; Ford et al., 2018; Urits et al., 2021), although numerous other phytocannabinoids exist within the plant at much lower levels. THC is viewed as the psychotropic cannabinoid, and gives users the acute effects associated with a "high" (euphoria, lack of coordination, relaxation; Bostwick, 2012), while CBD has been examined as an analgesic, anti-inflammatory, and neuroprotective agent (Ford et al., 2018).

Adverse Effects of Marijuana Use

Adverse effects of marijuana use are widely-reported, but largely poorly understood at this time. Effects can be broadly divided into acute and chronic and items with a strong evidentiary base of support and those supported only by low-quality evidence.

Many acute effects of marijuana use are dose-dependent (Ford et al., 2018), but a number of issues have been well-documented in the literature as well as anecdotally: loss of short-term memory, lack of coordination, reduced cognitive ability, tachycardia, reduction in impulse control, and hypertension (Bostwick, 2012; Clark et al., 2011; Ford et al., 2018; Franz & Frishman, 2016; Torres & Fiestas, 2012; Volkow et al., 2014). On higher doses, users may experience more "negative" effects of anxiety, paranoia, hallucinations, and confusion (Ford et al., 2018).

Shah and Fermo (2022) discuss some syndromic complications that can arise from cannabis use, but these do not appear to be commonplace. They include cannabis hyperemesis syndrome (CHS), which results from heavy cannabis use, which can have proemetic effects in some patients. This cyclical vomiting is related to daily cannabis use and will also be accompanied by nonspecific abdominal pain. Short-term treatment involves the usual anti-emetic medications and prevention of dehydration, while long-term treatment would involve weaning the patient off cannabis.

Another such syndrome is referred to as reversible cerebral vasoconstriction syndrome (RCVS). There is evidence that marijuana causes hypertension (Ford et al., 2018; Franz & Frishman, 2016), and one possible mechanism is through vasoconstriction. This syndrome causes "thunderclap" headaches and can trigger seizures. A study found that 30% of RCVS sufferers had a history of cannabis use, but the connection remains unclear (Shah & Fermo, 2022).

Martin (2020) evaluated risks associated with pregnancy and cannabis use. THC binds to two types of receptors in the body, known as CB1 and CB2 (Urits et al., 2021). CB1 receptors are found in the placenta and affect serotonin transport activity. This mechanism may alter newborn sucking reflex; CB1 receptors in the hippocampus of the newborn may also play a role in the development of normal sucking behavior. Animal studies have suggested that THC may negatively impact development of neonates; THC is known to decrease folic acid uptake, and lack of folic acid is known to be responsible for neural-tube defects (Martin, 2020). Breastfeeding while using marijuana is likely to pass metabolites to the feeding infant; THC is detectable in breast milk six days after use. Such exposures can lead to impulsive behavior and hyperactivity, as well as memory and IQ impairment.

An important potential long-term effect is the question of marijuana dependence (addiction). There is a cultural assumption that marijuana, unlike other common drugs of abuse, is not addictive. However, research indicates that users can become dependent on marijuana (Bostwick, 2012; Clark et al., 2011; Ford et al., 2018; Urits et al., 2021; Volkow et al., 2014). Studies have shown that approximately 9% to 10% of regular cannabis users will develop cannabis use disorder (Bostwick, 2012). Withdrawal from cannabis use resembles withdrawal symptoms for other substances, including irritability, sleep disturbance, dysphoria, anxiety, and cravings (Volkow et al., 2014). Cannabis use disorder can be a comorbidity with other substance use disorders or mental illnesses. These comorbidities may be mutually-reinforcing, complicating treatment options, which are primarily limited to the use of cognitive behavioral therapy (Ford et al., 2018).

Other long-term effects for which strong evidence exists include the following: amotivational syndrome, cognitive defects, and effects associated with inhalation of substances. Amotivational syndrome is characterized by a general apathy and lack of ambition to perform. Bostwick (2012) hypothesizes that because schizophrenia is often associated with high levels of the endogenous cannabinoid anandamide in the cerebrospinal fluid that THC may act in a similar fashion to trigger this symptom. Torres and Fiestas (2012) state that a cannabinoid-mediated lack of glutamate (an endogenous neurotransmitter) may likewise regulate emotions in a way that lead to this state of apathy.

Several authors have noted that chronic use of marijuana can lead to cognitive decline, some of which may be irreversible (Bostwick, 2012; Ford et al., 2018; Urits et al., 2021; Volker et al., 2014). Cognitive impacts include reduced attention span and information-processing capabilities, slowed reaction times, reduced decision-making ability, memory impairment, and increased impulsive behaviors. Urits et al. (2021) noted that such changes are related to dose, frequency, and duration of use of marijuana.

Many different dosage forms are currently available for medical cannabis, ranging from oils and tinctures to infused edibles, but the most popular forms remain the inhalant forms (metered-dose inhalers, “joints” [marijuana cigarettes]). Inhalation is popular due to its rapid activation, but it comes with its own unique set of hazards for the user. For patients who are already immunocompromised, smoking can irritate lung tissues and make them susceptible to infection and this can be an acute problem (Rosenthal & Kleber, 1999). More generally, many of the various nitrosamines, phenols, polycyclic aromatic hydrocarbons, reactive oxygen species, and other impurities taken into the lungs are toxic and carcinogenic. Chronic exposure can lead to the same kinds of problems that develop from exposure to tobacco smoke: bronchitis, asthma, emphysema, and lung cancer (Ford et al., 2018; Urits et al., 2021).

Limitations of Research

In part because users of cannabis may have pre-existing mental illnesses that they are treating by self-medication, the general relationship between the expression of schizophrenia and bipolar disorder to cannabis use is unclear. Some studies have found an association between the triggering of psychotic episodes and the development of schizophrenia with cannabis use (Bostwick, 2012), but others suggest that it may function as an antipsychotic (Clark et al., 2011).

Similarly ambiguous is evidence for serious cardiovascular events linked to cannabis use. Franz and Frishman (2016) point out that while an association appears to exist between marijuana and myocardial infarctions and coronary heart disease, studies have both supported and seemingly refuted such a connection. It is likely that because marijuana appears to have conflicting effects on cardiovascular activity, depending on dosage (Ford et al., 2018; Shah & Fermo, 2022), and more research will be required to further elucidate these questions.

If there is one area of agreement among the pro-medical use (Clark et al., 2011; Bostwick, 2012) and the anti-medical use (DuPont, 1999; Rosenthal & Kleber, 1999) advocates, it is that further research into chronic effects (and in some cases, acute effects) of marijuana use is vital to unlocking the unanswered questions that remain about cannabis use in the United States. Bostwick (2012) points out the historic roadblocks to conducting the basic science needed to gain a better understanding of this complex array of chemicals now being used as a pharmaceutical agent. The cannabis that is being grown at the University of Mississippi has long been the only legal source for researchers, and it is not representative of what users are taking today (Ford et al. [2018] describe the potency of "modern" joints as 15 times that of ones found in the recreational market in the 1960s and 1970s—the time when the marijuana at the University of Mississippi was first grown. Additionally, funding for marijuana research is generally only available from the National Institutes of Health (NIH), and competition for NIH grants is intense. Without further investigations, however, our understanding of the effects of cannabis on users is likely to remain stagnant.

Fortunately, one of the initiatives engendered by Louisiana's medical marijuana program is the promotion of new research projects by the flagship universities of Louisiana State University (LSU) and Southern University (SU), through their respective Agriculture Centers and partnerships with licensees who are growing and producing medical product for Louisiana's residents. Their latest reports are attached to this document as Appendices I and II.

Hemp with THC

Introduction

Signed into law in December 2018, the 2018 Farm Bill removed hemp (*Cannabis sativa* L.) and all hemp derivatives from the definition of marijuana in the Controlled Substances Act. As per Act 498 of the 2022 Louisiana Regular Session, regulatory authority of industrial hemp and consumable hemp products in Louisiana belongs to LDH. There, "industrial hemp" is defined as "the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a total delta-9 THC concentration of not more than 0.3 percent on a dry weight basis." A "consumable hemp product" is defined as "any product

derived from industrial hemp that contains any cannabinoid, including cannabidiol (CBD), and is intended for consumption or topical use." Research into the beneficial and adverse effects associated with cannabis use is ongoing, and results vary significantly from individual to individual, with both sets of effects requiring additional research as new cannabinoids are discovered and more is learned about the variety of effects cannabis users can experience. Studies involving cannabis use do not usually distinguish among consumable hemp, medical marijuana, legal marijuana, or illegal marijuana. Health effects from using these products are expected to be similar, but many such effects are dose-dependent.

Benefits

Consumers use hemp and hemp products for multiple reasons, but the most pertinent to LDH are the uses for nutrition, medication, and recreation. Both consumer reports and scientific study support positive benefits associated with the use of hemp and hemp products, although benefits are not equivalent across all research participants. Hemp is consumed for several nutritional reasons including its Omega-3 fatty acids, protein, magnesium, fiber, and vitamin profile (Ware, 2023; Nunn, 2023). Industrial hemp-derived cannabidiol products are used for multiple medical reasons. Studies have shown that CBD has the ability to offset anxiety and depression, treat epileptic seizures, reduce inflammation and pain, and treat addiction (Silva, 2023; Isles, 2021). Others support that CBD can be used to treat post-traumatic stress disorder, amyotrophic lateral sclerosis, arthritis, and diabetic symptoms (Silva, 2023). More studies explain how CBD may lower blood pressure, treat gastrointestinal disorders, or treat cancer and symptoms of chemotherapy (Isles, 2021). Additional hemp products, ones that contain delta-9 THC and/or other cannabinoids, have research supporting positive health benefits associated with use. These include treating anxiety, chronic pain, symptoms of epilepsy, cancer, side effects of chemotherapy, multiple sclerosis, insomnia, migraine, neuropathy, nausea, appetite loss, inflammation, arthritis, and inflammatory bowel syndrome (Silva, 2023; MacMillan, 2023).

Detriments

Despite support for extensive potential benefits of hemp product use, there is also research showing acute and long-term adverse health effects associated with the use of consumable hemp products, although adverse health effects are not equivalent across all research participants. There are adverse effects associated with hemp with THC (cannabis) use in adolescents and young adults. These include impaired learning and memory, reduced immediate recall and verbal reasoning, increased suicidal thoughts and attempts, and greater risk for developing mental health or psychotic symptoms and disorders (Sideli et al., 2021; CDPHE, 2023). Frequent cannabis use by young adults and adolescents is associated with developing psychotic symptoms in adulthood such as hallucinations, paranoia, and delusional beliefs as well as psychotic disorders in adulthood such as schizophrenia. The risk for these effects are greater among those who start using at an earlier age, use more frequently, and those with a family history of psychotic disorders (Sideli et al., 2021; CDPHE, 2023).

There are potential adverse effects associated with using industrial hemp-derived cannabidiol products. These include reduced alertness, changes in mood, decreased appetite, gastrointestinal symptoms, liver damage, and male reproductive harm. CBD may also produce cognitive impairment or psychotic effects in individuals who regularly use delta-9 THC products (SAMHSA, 2023). CBD products can interact with medications to produce unwanted effects. Taking CBD hemp products along with epilepsy medicines

may increase the risk of side effects. CBD products can have detrimental compounding effects with blood thinners, antidepressants, anxiety medications and pain medications (Nunn, 2023).

Short-Term Use Adverse Health Effects

There are several adverse health effects associated with short-term use of hemp products that contain cannabinoids in addition to CBD. Using hemp products can lead to a state of intoxication. The "high" feeling after cannabis use is variable and subjective. While intoxicated, individuals can experience euphoria, impaired motor coordination, anxiety, impaired judgement, or depression. Because cannabis impairs reaction time and motor skills, users are at an increased risk of motor vehicle accidents and injury from all causes when compared to past users or non-users. In both youth and adults, attention, working memory, and other cognitive functions like inhibition and problem solving are negatively affected by intoxication. The most common acute adverse effects are hallucination and panic attacks (Sideli et al., 2021). Some cases report severe allergy symptoms associated with hemp use, such as itching and swelling (Nunn, 2023). THC might harm developing fetuses, and use is discouraged in women who are trying to get pregnant, pregnant, or breastfeeding, as THC can transfer to the child in the womb and through breastfeeding (MacMillan, 2023). Other medical events associated with acute cannabis use include headache, throat irritation, insomnia, dizziness, nausea, diarrhea, seizure, syncope, and malaise (Health Canada, 2022). Individuals who use cannabinoid hemp products should take caution when also using prescription medication, as some medicines have known negative interactions with cannabis and others have unknown possible interactions. In addition, some studies give evidence that short-term cannabis use is associated with a greater risk of heart attack, especially from cannabis with higher concentrations of THC (CDPHE, 2023).

Long-Term Use Adverse Health Effects

There are several adverse health effects associated with long-term use of hemp products that contain cannabinoids in addition to CBD. Several studies have shown that long-term cannabis use is associated with cognitive impairment that can last as long as 25 days (Sideli et al., 2021). Prolonged use of cannabinoid hemp products may also lead to severe physical medical conditions. These include lung and testicular cancer; cannabinoid hyperemesis syndrome, characterized by severe abdominal pain and recurrent vomiting; chronic bronchitis, caused by lesions in the throat and lungs; and liver damage associated with negative interactions between cannabis and prescription drugs (Nunn, 2023; CDPHE, 2023). Long-term cannabis hemp users can become addicted, also known as cannabis use disorder. Addicted individuals can experience withdrawal symptoms when abstaining, including but not limited to depression, irritability, nervousness, restlessness, and sleep difficulties (Sideli et al., 2021; CDPHE, 2023). Additionally, many studies demonstrate that long-term regular use of cannabis is strongly associated with developing psychotic disorders such as schizophrenia. Individuals who use cannabis heavily over longer periods are associated with greater rates of new cases of psychotic disorders. On average, cannabis users experience the onset of psychotic disorders three to six years earlier when compared to individuals who never use. Patients with psychotic disorders who continue to use cannabis after their illness onset experience worse clinical outcomes than those who stop usage. Regular cannabis use and cannabis use disorders are also linked to an increased risk of manic episodes and bipolar disorder. The most vulnerable populations to these long-term psychotic effects are youth, adolescents, and individuals with family history of psychotic disorders (Sideli et al., 2021; CDPHE, 2023).

Adverse Health Effects through Contamination

The process of plant growth and product creation provides many opportunities for hemp flower and consumable hemp products to be exposed to harmful contaminants such as residual solvents, heavy metals, pesticides, and microbiological contaminants. Current hemp regulations require growers and producers to test their products for these variables before they are approved for sale. However, if proper protocol is not followed, or in the case of lab error, consumers run the risk of exposure to these harmful contaminants. Cannabis growers potentially use pesticides, and trace amounts could be found in products. Health effects of pesticides depends on the type of pesticide, but possible effects include nerve damage, skin and eye irritation, and cancer (EPA, 2023). During the process of growth, transportation, and production, hemp products could be exposed to microbiological contaminants. Effects of these can vary, with exposure to certain microbes leading to serious disease and other negative health outcomes (Sharma & Gilbert, 2018). Products must be tested for heavy metals, as exposure can lead to poisoning which may cause a variety of toxic effects on body tissues and organs (Balali-Mood et al., 2021). Hemp-synthesized intoxicants, such as delta-9 and delta-8 THC, are produced through semi-synthetic methods. These processes involve extracting CBD from hemp biomass, dissolving it in a solvent, and exposing it to an acidic catalyst and heat. Some solvents, such as heptane, are known toxins that can cause serious negative health effects in consumers (ATACH, 2023).

Conclusion

Research into the beneficial and adverse effects of cannabis on consumers is continuous, with new cannabinoids and new effects being discovered regularly. Effects on consumers are variable depending on cannabinoid levels, frequency of use, as well as the genetic, and medical history of the individual. Consumers use hemp products for many reasons, with nutrition, medication, and recreation being the most important to LDH. Research supports the nutritional value of consuming hemp for food; potential medical uses of CBD products such as for treating pain and depression; and potential medical uses of cannabinoid products that are not CBD exclusive such as for treating symptoms of epilepsy and multiple sclerosis. However, there is also extensive research supporting the link between cannabis use and acute and long-term adverse effects. Using hemp products risks exposing consumers to dangerous contaminants such as pesticides, heavy metals, residual solvents, and microbiological contaminants should proper protocol be unfollowed or in the case of laboratory error. Using CBD specific cannabis products is associated with possible acute effects including reduced alertness and gastrointestinal symptoms, as well as long-term effects such as liver damage, male reproductive harm, and negative compounding interactions with prescription medication. Using cannabis products that include cannabinoids in addition to CBD are associated with several acute and long-term negative health effects. Possible acute effects include intoxication, cognitive impairment, hallucination, and negative interactions with medication. Possible long-term effects include severe physical conditions such as cancer, cannabinoid hyperemesis syndrome, chronic bronchitis, and liver damage, as well as severe mental conditions such as cannabis use disorder, bipolar disorder, and schizophrenia. Additional research will be required to better establish causal linkage between acute and long term use of the variety of cannabis products, and proper, adaptable regulation will be necessary to uphold the most efficient and safe cannabis market within Louisiana.

Kratom

Introduction

Kratom commonly refers to an herbal substance that can produce opioid- and stimulant-like effects. Kratom refers to both Mitragyna speciosa, a tree native to Southeast Asia, and to products derived from its leaves that are marketed as herbal supplements. Kratom leaves contain many chemical compounds (known as bioactive alkaloids) that can affect the body. The well-studied compounds related to kratom are mitragynine and 7-hydroxymitragynine (UN, 2021). Kratom and kratom-based products are currently legal and accessible in many areas, though the United States and international agencies continue to review emerging evidence to inform kratom policy (UN, 2021). While kratom or its related compounds have not been approved by the U.S. Food and Drug Administration as safe and effective for any medical use, people report using kratom products to alleviate drug withdrawal symptoms and cravings (particularly for opioids), to alleviate pain and to help manage mental health problems (Palamar, 2021; Garcia-Romeu et al., 2020; Grundmann, 2017).

Much is still unknown about chemical compounds related to kratom, the short- and long-term health and safety impacts of kratom use and kratom's potential therapeutic uses. The National Institute on Drug Abuse (NIDA) supports and conducts research to evaluate potential medicinal uses for kratom and related chemical compounds. NIDA also supports research towards better understanding the health and safety effects of kratom use. NIDA is particularly interested in studying how kratom use may impact opioid use, which continues to drive the drug overdose epidemic in the United States. Rare but serious effects have been reported in people who use kratom, including psychiatric, cardiovascular, gastrointestinal and respiratory problems. (UN, 2021; Leong Bin Abdullah & Singh, 2021). Compared to deaths from other drugs, a very small number of deaths have been linked to kratom products and nearly all cases involved other drugs or contaminants.

History of Kratom

Anthropologists report that kratom has been used in Southeast Asia for hundreds of years as a multi-purpose remedy in traditional medicine, to increase alertness and energy while working and during social gatherings (UN, 2021; Henningfield et al., 2019). While estimates of the scope of kratom use in the United States vary, (UN, 2021) the expansion of kratom vendors and increasing case reports suggest kratom use has become more common over the past two decades (Prozialeck et al., 2012).

Effects of Kratom Use

People typically use kratom by swallowing raw plant matter in capsule or powder form, mixing kratom powder into food or drinks, brewing the leaves as a tea, or taking liquid kratom extract (UN, 2021). People who use kratom report both stimulant-like effects (increased energy, alertness and rapid heart rate) and effects that are similar to opioids and sedatives (relaxation, pain relief and confusion) (Leong Bin Abdullah et al., 2019; Singh et al., 2019). Studies and case reports have also indicated rare adverse effects may be associated with kratom or individual kratom compounds (UN, 2021). While many people who use kratom report that smaller doses of kratom produce stimulant-like effects and larger doses produce opioid- or sedative-like effects, (Grundmann, 2017) studies have not yet established how these

effects depend on the amount consumed or method of consumption (Leong Bin Abdullah et al., 2019; Singh et al., 2019).

Researchers are still learning how kratom and kratom compounds affect the body, as well as how short- and long-term kratom use may impact health. While evidence is quickly evolving, early studies have revealed important information about how the drug works. Like all drugs, kratom's effects may depend on the amount taken, potency (concentration and strength), formulation of the product, the way it is ingested, other drugs in a person's system, a person's underlying medical conditions, and a person's previous experience with the substance, among other factors (Garcia-Romeu et al., 2020; Grundmann, 2017; Singh et al., 2019). Importantly, kratom products vary and effects are difficult to predict. Some kratom products have been found to contain contaminants that produce effects not associated with kratom or kratom compounds alone (Post et al., 2019; Kronstrand et al., 2011; Dixon et al., 2019).

Mitragynine, 7-hydroxymitragynine, and other kratom compounds drive these effects. The effect of kratom products can vary depending on the concentration and combination of specific kratom compounds within the product. While kratom leaves contain many chemical compounds that may influence the human body, the most well-studied is mitragynine. When ingested, mitragynine breaks down into another chemical called 7-hydroxymitragynine, which also influences the body and is an important subject of research (Eastlack, Cornett & Kaye, 2020).

Adverse effects range from mild to severe. Some people who use kratom have reported mild side effects, such as nausea, constipation, dizziness, and drowsiness. (Garcia-Romeu et al., 2020; Grundmann, 2017). In case reports, clinicians report seeing patients with a wide range of rare but serious adverse effects associated with kratom exposure—including mental and neurological symptoms (confusion, tremors and seizures), heart and lung problems (high blood pressure and slow breathing), gastrointestinal problems (nausea and vomiting) and, liver problems (UN, 2021, Graves et al., 2021). A very small number of deaths have been linked to kratom products, and nearly all cases involved other drugs or contaminants (UN, 2021, Post et al., 2019; Kronstrand et al., 2011; Henningfield et al., 2019; Dixon et al., 2019; Eggleston et al., 2019).

Drug interactions may influence effects. Studies suggest many people who use kratom also use other drugs and have conditions for which medications are often prescribed (Garcia-Romeu et al., 2020; Grundmann, 2017; Singh et al., 2019). Case reports suggest using kratom in combination with other drugs (sometimes called polysubstance use) may produce severe adverse effects, such as liver problems or even death (Veltri & Grundmann, 2019). More research is needed to better understand the impact of using kratom in combination with other substances.

Long-term health effects are not well understood. Because kratom research is relatively new compared to more widely used drugs, there is little evidence to determine how kratom use may affect someone over time. Case reports do show regular, long-term, kratom use in large amounts may be associated with serious liver problems. These cases appear to occur unpredictably in a small minority of people who use kratom, and it is unclear what role other substances and underlying health conditions may play (UN, 2021; Schimmel & Dart, 2020). Researchers are also still learning how often and to what extent people who use kratom experience withdrawal or substance use disorder symptoms related to kratom use.

Research on potential therapeutic effects of kratom is ongoing. Researchers have not proven kratom to be safe or effective for any medical purpose, though kratom has been used in traditional medicine (Cinosi et al., 2015). Many people who use kratom products report doing so to self-treat pain, anxiety, depression, fatigue, and drug cravings and withdrawal symptoms (especially related to opioid use) (UN, 2021, Garcia-Romeu et al., 2020).

To help inform kratom policy and health decision-making around kratom use, NIDA conducts and supports research on how kratom compounds work in the brain, as well as research on kratom use patterns, health effects, therapeutic uses, and drug interactions. Because many people who use kratom also report using or previously using opioids and experiencing opioid use disorder, (Palamar, 2021; Garcia-Romeu et al., 2020) NIDA is particularly interested in studying how kratom use may impact opioid use, which has driven the drug overdose epidemic in the United States. Early studies have found that some people report using kratom to ease craving and withdrawal symptoms associated with other substances, including opioids and stimulants (Leong Bin Abdullah & Singh, 2021; Smith et al., 2021; Vicknasingam et al., 2010; Saref et al., 2020; Smith & Lawson 2017; Boyer, Babu and Macalino, 2007).

NIDA and the National Institutes of Health (NIH) HEAL (Helping to End Addiction Long-term®) Initiative are supporting several studies evaluating kratom and related compounds as potential treatments for chronic pain and for opioid withdrawal and opioid use disorder. One of these projects (also supported by the National Center for Advancing Translational Sciences and National Institute of Neurological Disorders and Stroke) includes efforts to help develop new medications, including kratom-derived products, as potential treatments for opioid use disorder. NIDA conducts and supports research to better understand how often and to what extent people who use kratom experience withdrawal and substance use disorder symptoms related to kratom use.

To be diagnosed with a substance use disorder, a person must meet specific diagnostic criteria for continued, compulsive substance use despite negative consequences. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)—a reference text published by the American Psychiatric Association that health professionals use to diagnose substance use disorders and other psychiatric disorders—does not include a specific diagnosis related to kratom use (APA, 2013). However, some researchers studying kratom have modified criteria to study kratom use patterns and symptoms that resemble other substance use disorders (Garcia-Romeu et al., 2020).

Studies suggest people may experience mild to moderate withdrawal symptoms when they stop regular kratom use, (Stanciu et al., 2019; Singh et al., 2018) but more research is needed to understand to what extent people develop substance use disorder symptoms related to kratom (UN, 2021; Garcia-Romeu et al., 2020). Preliminary data from anonymous surveys of people who use kratom suggest a minority of people report experiencing kratom-related withdrawal symptoms and a smaller minority report experiencing substance use disorder symptoms related to kratom use (Garcia-Romeu et al., 2020). Some experts are concerned about kratom's addictive potential because the main kratom compounds, mitragynine and 7-hydroxymitragynine, partially activate the same receptors (specific molecular structures on the surface of nerve cells) in the brain on which drugs with known addictive properties act. However, researchers have observed that the way kratom compounds activate these receptors may reduce the potential for addiction relative to opioids (Kruegel et al., 2016; Váradi et al., 2016; Matsumoto et al., 1996; Hanapi et al., 2021). Further, studies in animal models indicate that the addictive potential of mitragynine and 7-hydroxymitragynine may differ from one another (Hemby et al.,

2019). Further research is needed to better understand how various compounds related to kratom interact to influence the risk of withdrawal and addiction.

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Appendices

Appendix 1

7/3/2023
Health and Welfare Committee 900 North Third Street
Baton Rouge, LA 70802

In accordance with La R.S. 40:1046(H)(2)(a), the following report outlines the LSU AgCenter's research initiatives relative to therapeutic cannabis.
LSU AgCenter Cannabis sativa Research Report for Health and Welfare Committee

Currently, the LSU AgCenter funds therapeutic Cannabis, industrial hemp, and other medicinal plants research through the Therapeutic Cannabis Research Committee (TCRC). The committee reviews proposals and allocates funds to researchers whose projects are approved. To date, the total funding approved amounts to $1,351,096.07 across 21 projects. The projects range from molecular breeding projects, the use of cannabis in treatment of neurodegenerative disorders in animal models, the effect of Cannabis use on substance abuse disorders, the potential use of Cannabis to treat heart diseases, identification of best practices for hemp production, development of IPM and fertilization regimens, the investigation of the nutritional value of hemp greens, and exploration of hemp for use in textiles. These projects are all detailed below. The TCRC has recently put out a call for white papers to further broaden the scope of research on therapeutic Cannabis use.

Projects funded by the Therapeutic Cannabis Research Committee Total Funding: $1,351,096.07
Number of Projects: 21

1. Title: Development of SNP panels for THC and CBD traits in Cannabis species
    a. Funding: $47,694.00
    b. Summary: Develop molecular markers using SNP panels for future use in Cannabis breeding aiming for the differentiation between high CBD plants and high THC plants to make it easier to develop those varieties. Markers for sexing of plants have been developed using these panels. Further cannabinoid profiling and development of markers looking at disease and pest resistance, stress, and terpene profiling is also planned.

2. Title: Use of Zebrafish Models to Investigate the Neuroprotective/Neuro- restorative

Potential of Target Cannabinoid Extracts and Mixtures on Select Neurodegenerative Disorders

   a. Funding: $55,750.00
   b. Summary: Using zebrafish as a model organism to study the effects of Cannabis extracts on neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Cannabinoids are known to have neuroprotective benefits because of anti-inflammatory and antioxidant activity. Zebrafish adults, embryos, and larvae are being treated with cannabinoid mixtures to study their neurological effects.

3. Title: Developing Arthropod Models for Studying Interactions of the Cannabinoid Receptor and Neurodegenerative Diseases
   a. Funding: $94,477.00
   b. Summary: Human cannabinoid receptors have been knocked into arthropod species using a genetic modification technique. These insects are being used as a model organism to study cannabinoid effects on slowing or halting the progression of diseases like Alzheimer's, Parkinson's, spastic paraplegia, and schizophrenia. Mobility and electrophysical assays are investigating the effects on neurodegeneration and improving organism longevity.
4. Title: Evaluation of container grown hemp and herbicide evaluation
   a. Funding: $22,674.16
   b. Summary: Master's project investigated the feasibility of using containers for hemp production in Louisiana. Some objectives of the research were to identify the ideal container size for promoting hemp growth, identifying the optimal planting density, comparison of growth media types, compare the effect of container color on soil temperature and the effect on the hemp plants, and identification of effective herbicide treatments.
5. Title: Initial Steps in Identifying the Components of a Hemp IPM Program
   a. Funding: $39,960.00
   b. Summary: Initial study of insect pest populations that are prevalent in hemp production of Louisiana to determine the pests with the biggest economic impact. Insect monitoring methods are also being evaluated in greenhouse and field settings. The effect of key hemp insect damage on cannabinoid production is another research focus, as it is important to maintain hemp compliance and avoid crop destruction due to high THC levels.
6. Title: Evaluation of commercial cultural practices for Louisiana grown industrial hemp
   a. Funding: $31,001.00
   b. Summary: Master's project evaluating germination and transplant production practices, in-field plant spacing with the goal of producing best management practices guide for industrial hemp in Louisiana.
7. Title: A novel goat model to characterize the male fertility following paternal cannabidiol exposure
   a. Funding: $50,000.00
   b. Summary: Study looking at the effect of CBD exposure on the effect on goat semen attributes and sperm RNA code as an animal model. As Cannabis gains

social acceptance, the applicability of an animal model could reveal details on CBD safety for humans.

8. Title: Identification and quantitation of bioactive compounds in hemp used as a salad green
    a. Funding: $49,500.00
    b. Summary: Investigating the nutraceutical value of hemp microgreens as a salad green or other value-added food products. Cannabinoid testing will determine the amount of cannabinoids present in the leaves including THC, THCA, CBD, CBDA, CBG, and CBGA. Antioxidant and vitamin content will also be quantified. A taste test will also evaluate the marketability as a food product compared to other leafy green vegetables.
9. Title: Assessing interactions in the capacity of terpenes to produce anti-inflammatory and antinociceptive effects as well as reduce the abuse-related effects of opioids
    a. Funding: $77,964.00
    b. Summary: Evaluate the effect of terpenes and their effects on their ability to reduce inflammation, produce analgesic effects, and reduce opioid use. Three prevalent terpenes will be used to evaluate effects on inflammatory signaling pathway and antinociception. Fentanyl-induced place conditioning will be utilized in a mouse model to evaluate the effects on opioid abuse.
10. Title: The impact of endocannabinoids on oviduct and uterine fluid composition regulation and early embryo development in vitro
    a. Funding: $89,132.00
    b. Summary: Utilize cutting edge cell culture modeling approaches to elucidate the influence of cannabis metabolites on oviduct and uterine fluid composition in vitro. THC and CBD will be combined at different levels as factors in the experimental design to determine their influence during the early stages of pregnancy.
11. Title: Container grown Cannabis sativa ssp. for essential oil production in Louisiana
    a. Funding: $25,516.24
    b. Summary: Continued research to evaluate the efficacy of high-tunnel production of Cannabis grown in containers for oil production. Experiments designed to optimize production methods to assess the impact of different factors like container size, container color, planting density, and media types.
12. Title: Establishment of a centralized Cannabis plant material propagation system for continued hemp research
    a. Funding: $22,500.67
    b. Summary: Funding provided to establish a room dedicated to Cannabis propagation and the production of clones as a source of plant material for various LSU research projects. The establishment of this project will also be used to generate funding to maintain the room and cover costs of supplies and plant material moving forward.

13. Title: In vitro and in vivo screening of native plant crude extracts again major plant pathogens affecting Cannabis and specialty food crops of Louisiana

    a. Funding: $6,135.00
    b. Summary: Exploratory study to evaluate the effects of extracts sourced from selected Louisiana native plants on fungal and bacterial pathogens of Cannabis using in vitro bioassays.
14. Title: Evaluation of greenhouse grown Cannabis sativa for essential oil production in Louisiana.
    a. Funding: $84,659.00
    b. Summary: Evaluation of eight different varieties of Cannabis produced in greenhouses for essential oil production. Varieties will be sourced based on performance from past trials as well as from the USDA germplasm bank. Data collected will be done in accordance with USDA protocol and made publicly available for future researchers.
15. Title: A novel goat model to characterize the male fertility following paternal cannabidiol exposure
    a. Funding: $84,638.00
    b. Summary: Renewal of previously funded study to create to further explore and create a more thorough data set on the effect of CBD on goat semen attributes. The larger data set will allow for better analysis and acquisition of potential funding from external sources.
16. Title: Consumer Acceptance of Industrial Hemp Textile Products: Education and Outreach
    a. Funding: $96,100.00
    b. Summary: Consumer acceptance survey to determine willingness to pay for hemp textile projects compared to other alternative fabrics and discover consumer attitudes towards hemp-based products. Education of consumers about the possibilities of hemp textiles will occur through hemp textile product exhibition.
17. Title: Assessing the impact of Cannabis on executive function and susceptibility to stimulant addiction
    a. Funding: $183,626.00
    b. Summary: Clinical pilot study looking at the effects of Cannabis on the effect of methamphetamine vulnerability and use. Specific cannabinoids and terpenes will be utilized to identify and isolate the effect of different compounds on methamphetamine use and to determine if Cannabis use may influence outcomes related to co-occurring stimulant use disorder. The impact of therapeutic cannabis use on executive function will also be investigated.
18. Title: Exploring the Markets for Hemp Fiber Textile Products
    a. Funding: $67,420.00
    b. Summary: Systematic data mining of the consumer market to examine hemp products and hemp-based textiles to identify effective market determinants for promotion of hemp textiles and clothing. Surveys will also be conducted to best identify consumer acceptance variables. Development of hemp textiles and prototypes for further market testing and to help hemp textile entrepreneurship.
19. Title: The effect of cannabidiol on the heart after myocardial infarction
    a. Funding: $138,800.00

    b. Summary: Study of the role of cardioprotective effects of Cannabis and CBD to evaluate potential therapeutic potential in treating heart diseases. Mechanisms of cardioprotective effects will be evaluated using single-cell multi-omics to look at gene expression and epigenetics. Mice will be used as a translational animal model to elucidate gene regulatory networks and transcription factors to identify differentially expressed genes.
20. Title: Optimizing Louisiana planting and harvest dates for field grown day-neutral hemp 'Pipeline' crops in the fall and early spring seasons
    a. Funding: $20,209.00
    b. Summary: Study to explore alternative planting dates for Louisiana industrial hemp production during cooler seasons for production of day-neutral cultivars. The hypothesis is that planting during less extreme climatic conditions may alleviate disease and insect pressure and improve yields.
21. Title: Soil Fertility and nutrient Management Research for Hemp Production in Louisiana
    a. Funding: $130,760.00
    b. Summary: Identification and establishment of fertilizer and nutrient management approaches for key nutrients in hemp production in Louisiana growing conditions. A database of yield limiting nutrients in hemp production will be used to help establish optimal fertilizer rates of major essential nutrients for optimal hemp production. Fertilizer effects on nutrient content, pest and disease pressure, and cannabinoid production will also be explored.

Appendix 2

Southern University Agricultural Research and Extension Center

Hemp and Therapeutic Use Research Projects

Industrial Hemp Projects

2021-2023

1. Establishment of sustainable hemp production best practices and management strategies for small farmers in the state of Louisiana.
    a. Black Farmers Hemp Group (Lafayette, LA)
    b. Davis Farms (Waterproof, LA)

    Summary: The contractors assisted with the hemp research plots to include 1) land/soil preparation, 2) maintenance, directed by SU Ag Researchers, 3) seed/biomass harvest and 4) data generation and collection.

2. Establishment of Industrial Hemp Research Plot at Southern University Ag Center's Horticultural Farm

    Summary: Preliminary data suggests that industrial hemp has promising potential as an agronomical crop in the state of Louisiana. Our research indicates that all seven hemp varieties grew quickly and performed well when they were able to outcompete weeds. Weeds and increased rainfalls were a couple of the nuisances encountered while conducting this research. Moving forward, we have plans to measure precipitation and temperatures during the growing season. Variations in genetics, soil, weather, and other growing conditions resulted in variations in yield and quality.

Proposed Therapeutic Use Projects

1. Title: Evaluation of cell viability of rat liver cells following independent and combined cannabinoid and terpene extract applications.

    Summary: The aim of this study is to assess cell viability and evaluate the anti- inflammatory effects of cannabinoids and terpenes, two classes of compounds derived from the cannabis plant, on rat liver cells. Cannabinoids are molecules that interact with the endocannabinoid

system (ECS), a modulatory system that regulates various physiological processes, including inflammation, metabolism, and liver function.

2. Title: Preclinical Evaluation of Cannabinoid-Infused Products for Wound Healing in Swine

   Summary: Cannabinoids have shown promise in promoting anti-inflammatory, analgesic, and tissue-regenerating effects. Incorporating these compounds into various product formulations could offer a unique and novel therapeutic approach for enhancing wound healing outcomes.

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